UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY, and)))
MANULIFE INSURANCE COMPANY (f/k/a)
INVESTORS PARTNER INSURANCE COMPANY),	Civil Action No. 05-11150-DPW Hon. Judge Douglas P. Woodlock
Plaintiffs,)))
vs.)
ABBOTT LABORATORIES,)
Defendant.)

CORRECTIONS TO THE AFFIDAVIT OF STANLEY BUKOFZER, M.B., B.CH., M. MED. (INT. MED.)

Abbott Laboratories ("Abbott") respectfully submits these corrections to the Affidavit of Stanley Bukofzer, M.B., B.Ch., M. Med. (Int. Med.). Exhibit 614 was inadvertently referred to in the affidavit as Exhibit EC. The affidavit has been corrected to include references to Exhibit 614 instead of Exhibit EC and is attached. Abbott is also attaching a true and correct copy of Exhibit 614 with the correct cover sheet. Additionally, the second half of Exhibit 608 was inadvertently not included when the Affidavit was originally filed. Abbott is attaching Exhibit 608 with the missing pages included. These are the only corrections to the Affidavit of Dr. Bukofzer. Abbott will provide the court with courtesy copies of Dr. Bukofzer's affidavit with these corrections on Monday, March 10, 2008.

Dated: March 10, 2008

Respectfully submitted,

ABBOTT LABORATORIES

By its attorneys

/s/ Jeffrey I. Weinberger

Jeffrey I. Weinberger

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CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on March 10, 2008.

Date: March 10, 2008.	
	/s/ Ozge Guzelsu

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY and MANULIFE INSURANCE COMPANY,

CIVIL ACTION NO. 05-11150-DPW

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

AFFIDAVIT OF STANLEY BUKOFZER, M.B., B.Ch., M. Med. (Int. Med.)

- I, Stanley Bukofzer, hereby declare and say:
- 1. My name is Stanley Bukofzer. I am over 18 years of age, and suffer from no condition or disability that would impair my ability to give sworn testimony. This affidavit is based upon my own personal knowledge.

Education and Professional Background

- 2. I am currently employed by Astellas Pharma U.S., Inc. as Vice President of Medical Affairs. From 1996 until June 2007, I was employed by Abbott Laboratories ("Abbott").
- 3. I was born in South Africa. I received my undergraduate degree as Bachelor of Medicine and Bachelor of Surgery from the University of Witwatersrand in

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Johannesburg, South Africa in 1979. I subsequently specialized in internal medicine and received my postgraduate medical degree as Master of Medicine from the University of Witwatersrand in 1986. I was in academics and private practice until joining Abbott in mid-1996 as Medical Director for Abbott's South African affiliate, part of Abbott's International Division.

Document 362-2

4. At the end of 1998, I was transferred to the Abbott International Division in Abbott Park, Illinois, as Associate Medical Director for Urological Products and later promoted to Medical Director. I remained in that position until approximately late March or early April 2001, when I was appointed Head of Abbott's Anti-Infective Venture. In August or September 2003, as a result of a change in company structure, I was named Global Project Head for Anti-Infectives. My role remained substantially the same as they had been in my previous position. In August or September 2004, I was promoted to Divisional Vice President of Global Medical Affairs, the position in which I remained until I left Abbott in 2006 to take up my present position.

Responsibilities as Head of Abbott's Anti-Infective Venture

5. When I became Head of the Anti-Infective Venture in March or April 2001, the venture had two compounds under development: (1) ABT-773, a ketolide antibiotic; and (2) ABT-492, a quinolone antibiotic. It was my responsibility as venture head to supervise and lead the team of professionals responsible for the development of these compounds. Among other things, my responsibility involved supervising Abbott's ABT-773 clinical study program and Abbott's efforts to receive approval of ABT-773 from the FDA and other regulatory agencies by ensuring that the benefit-to-risk ratio of the compound met the requirements of these agencies. It was also my responsibility to make

presentations regarding the status and development of ABT-773 to Abbott's senior management, including at meetings of the Pharmaceutical Executive Committee ("PEC") and at portfolio reviews.

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- 6. I was informed that I would become Head of the Anti-Infective Venture several weeks before taking over that position. From the time in February 2001 when I was told that I was going to be appointed Head of the Anti-Infective Venture through at least mid-2002, I spent an average of more than 50% of my time on ABT-773-related work.
- 7. In order to be able to fulfill my duties and responsibilities in supervising the development of ABT-773, during the transitional period of the last week of February and March 2001, prior to becoming venture head I worked to familiarize myself with the status of the compound. In order to do so, I read documents regarding the history, status and development of ABT-773 provided to me.
- 8. During this transitional period, I reviewed materials provided to me by my future boss, Dr. Eugene Sun, Abbott's Divisional Vice President for Anti-Viral and Anti-Infective Development, and by a few members of the existing ABT-773 team in order to allow me to become familiar with the program for which I would soon be responsible. For example, by email dated February 22, 2001, Dr. Sun sent me several key documents prepared by Abbott's ABT-773 team, including (1) Abbott's ABT-773 Development Plan; (2) an ABT-773 "Update" memorandum; (3) an ABT-773 Update presentation by the ABT-773 program to Abbott's senior management dated February 12, 2001; (4) an ABT-773 Portfolio Review presentation dated December 5, 2000; (5) a Contact Report regarding the ABT-773 End of Phase 2 Meeting with the FDA, held on November 27, 2000; and (6) Abbott's November 27, 2000 ABT-773 End of Phase 2 presentation to the

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FDA. I read each of these documents after I received them. Attached hereto as D's Exhibit 608 is a true and correct copy of Dr. Sun's email to me of February 22, 2001, together with the documents that were attached to the email. I reviewed each of the documents regarding ABT-773 I received during this transitional period from Dr. Sun and other Abbott employees in detail.

9. During the week before I assumed leadership of the Anti-Infective Venture, I also met extensively with experienced members of the existing ABT-773 team to learn as much as I could about the status and development of the compound. For example, I met with Dr. Carl Craft, my predecessor as Head of the Anti-Infective Venture, for approximately three hours per day over a period of about a week, to obtain as much information from him as I could regarding the ABT-773 development program and the functioning of the venture. I also met with Dr. Craft's direct reports who were to become my direct reports, including Dr. Linda Swanson, at that time the director of the ABT-773 clinical research team to whom the project managers reported; Carol Meyer, the director of operations for ABT-773, who also additionally later assumed Dr. Swanson's responsibilities; and all of the medical directors for the ABT-773 program. Soon after becoming venture head, I also met with Jeanne Fox and Greg Bosco of Abbott's regulatory affairs group to discuss the status of ABT-773, Abbott's contacts with the FDA regarding ABT-773, and the regulatory environment in which ABT-773 was being developed. I also met with Rod Mittag of Abbott's commercial group with regard to ABT-773. I relied upon the information I received from these discussions with members of the ABT-773 team in fulfilling my responsibilities in the ordinary course of business as Head of the Anti-Infective Venture and in supervising the development of ABT-773.

- 10. In order to fulfill my duties and responsibilities as Head of the Anti-Infective Venture to supervise the development of ABT-773, I needed to become and stay fully informed of the status and of all significant developments with regard to the ABT-773 program. As a result of my extensive discussions and meetings with Abbott employees regarding ABT-773 and my review of key ABT-773 documents during February, March and April 2001, at the time I became Head of the Anti-Infective Venture in April I was and considered myself generally well informed with regard to the status and development of ABT-773 at that time and with the major issues that needed to be addressed as part of the ABT-773 development program, including clinical and regulatory questions, among others. During my tenure as venture head, I continued to meet on a daily basis with members of the ABT-773 team and to review documents and data regarding all aspects of the program. I relied upon the information I received in the ordinary course of business from the ABT-773 team and from ABT-773 documents both before and after I became venture head in my work and decision-making regarding the ABT-773 program and in meetings with and to make presentations to Abbott's senior management with respect to the status of and developments on the program.
- 11. As Head of the Anti-Infective Venture in 2001 and 2002, I reported directly to Dr. Sun, who in turn reported to Dr. John Leonard.
- 12. The Anti-Infective Venture employees reporting directly to me as the supervisor of the ABT-773 program included the head of the ABT-773 clinical team (Dr. Swanson), the head of the ABT-773 operations team (Ms. Meyer), and the medical directors. Other Abbott employees who worked on the ABT-773 team and reported to me indirectly or on a "dotted-line" as part of the matrixed team included chemists who worked to develop the

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drug substance and the formulation of the compound, microbiologists and regulatory experts, including Jeanne Fox, the head of Abbott's Anti-Infective Regulatory Affairs group, as well as representatives of other functions.

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13. Prior to and during most of the time I was responsible for supervising the development of ABT-773 during 2001 and 2002, the venture regularly generated in the ordinary course of business monthly reports that updated the status of the development of ABT-773. The monthly report for ABT-773 was prepared and circulated at the end of each month. Thus, for example, the March 2001 monthly report would have been prepared and circulated at the end of March 2001. The monthly status reports were usually prepared by Carol Meyer in her capacity as head of ABT-773 operations, with input from other members of the ABT-773 team. I did not prepare the monthly status reports myself, but it was my practice as venture head to review in the ordinary course of business each of the monthly status reports before they were finalized and to ensure that they were accurate and complete to the best of my knowledge. Attached hereto as D's Exhibits 613, 638 and 654 are what I believe to be true and correct copies of examples of the ABT-773 monthly status reports that I reviewed in performing my duties as venture head, from April 2001. These examples are for March 2001 (D's Exhibit 613), May 2001 (D's Exhibit 638), and July 2001 (D's Exhibit 654), respectively. Reports in the same or similar format were generated by the ABT-773 program in the ordinary course of business before I became venture head, and I reviewed and relied upon some of these earlier monthly status reports as part of the process in February and March 2001 of becoming informed about the status and development of ABT-773, as described above.

ABT-773: Status and Development As of April 2001

- 14. ABT-773 is a member of the new ketolide class of antibiotics, which is in turn related to the macrolide family of antibiotics. As Head of the Anti-Infective Venture, I learned that antibiotics is a competitive field, in which macrolides and quinolones compete against older forms of antibiotics, such as cephalosporins, erythromycin and penicillin, for the treatment of community acquired microbial infections.
- 15. I understand that ABT-773 was approved by Abbott's senior management in March 1997 as a candidate for development by Abbott's Anti-Infective Venture. When I became Head of the Anti-Infective Venture, the ABT-773 adult oral formulation program had entered into Phase III of the compound's development, though certain Phase I and Phase II trials regarding aspects of the program were still in progress or were being planned.
- 16. At the time that I became Head of the Anti-Infective Venture, the ABT-773 adult oral formulation was being developed for four indications: (1) Acute Bacterial Exacerbation of Chronic Bronchitis ("ABECB"); (2) Acute Bacterial Sinusitis ("ABS"); (3) Acute Streptococcal Pharyngitis/Tonsillitis ("Pharyngitis"); and (4) Community Acquired Pneumonia ("CAP").
- 17. At the time I became Venture Head, based on my review of ABT-773 documents and discussions with members of the ABT-773 team, as discussed above, and based on my experience in the industry, I was optimistic in April 2001 about the prospects for the compound, although I recognized that, as with all drugs, there would be challenges, both known and unknown, in bringing the compound to market.

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18. When I became Head of the Anti-Infective Venture in April 2001, I was aware from my review of the documents of issues that would need to be addressed during the development of ABT-773. These issues included the potential for liver toxicity and the potential for QT interval prolongation (which can sometimes be associated with arrhythmias). I was aware that both issues would be examined by the FDA for any antibiotic under development. As noted above, by that time I had reviewed the Abbott's end of Phase II data regarding the Phase II studies that had been completed as of the end of 2000. I had also reviewed Abbott's contact report regarding the November 27, 2000 End of Phase II meeting with the FDA, as well as internal memoranda referencing the FDA's focus in general on possible safety issues. Based on my experience in the industry, at the time I became venture head I understood that the FDA and other agencies were going to expect Abbott to supply adequate data to establish that ABT-773 would be safe and effective for use in the patient populations we intended to treat; as the FDA would expect for any drug in development. I further understood that there was a general FDA concern as to whether ketolides (derived from macrolides), such as ABT-773, would have an effect similar to or greater than macrolides with respect to there being a class effect on OT intervals or on liver toxicity. However, none of the information I had learned about ABT-773 itself caused me to doubt that the drug was likely to have a positive benefit-to-risk ratio, given that there was no data that I had seen that led me to believe that there was a specific disqualifying safety issue, either on the part of Abbott or the FDA. In other words, I did not believe at the time I became venture head that the

regulatory challenges faced by ABT-773 were any more significant than the regulatory challenges faced by any other drug of a new antibiotic class.

- 19. Based on my discussions with Abbott employees and my review of Abbott documents, including two white papers prepared by Abbott's clinical team, including medical directors, for the End of Phase II meeting with the FDA, I understood as of the time I became venture head in or around early April 2001 that Abbott's clinical team did not believe ABT-773 had any QT prolongation or hepatotoxicity issues that could reasonably be expected to have a material adverse effect on the ABT-773 program.
- 20. I was aware when I became Head of the Anti-Infective Venture that the FDA had raised concerns regarding liver toxicity issues in general. In fact, I learned during the period before I became Venture Head, from reading an ABT-773 Update dated February 12, 2001 provided to me by Dr. Sun, that the FDA had a meeting on guidance to the industry on how to study the potential for liver toxicity in mid-February 2001.
- 21. I therefore understood when I became Head of the Anti-Infective Venture that Abbott would have to show the FDA that ABT-773 would be safe with regard to not causing liver abnormalities that were unacceptable with respect to extent or severity. I also understood from the documents I had reviewed and my discussions with the ABT-773 team that Abbott had provided information to the FDA regarding liver function issues. However, I had not seen any data in the spring of 2001 that suggested that there was any specific concern at Abbott or from the FDA about ABT-773 itself with regard to liver issues and. In addition, I was aware that the fact that other antibiotics, in particular macrolides, had demonstrated some liver toxicity issues but had not been removed from the market.

- 22. At or around the time I became Head of the Anti-Infective Venture, I learned that Abbott had observed some evidence of possible liver toxicity among Japanese patients in an early study of ABT-773 conducted in Hawaii. I was also aware from my review of documents and discussions with ABT-773 team members that Abbott had repeated the study and similar results were not seen in that or any other study. D's Exhibit 608 at ABBT205044. A true and correct copy of the February 12, 2001 ABT-773 Update Presentation is attached hereto as D's Exhibit 607 and also reflects that conclusion at ABBT205064. Accordingly, the program under my direction would continue to monitor liver function toxicity data in Phase III clinical studies, but as of the time I became venture head, I had concluded, consistent with what I had been informed by the ABT-773 team, that there was no evidence from the clinical program to date to suggest that there were any issues for ABT-773 with regard to liver toxicity that would jeopardize approval. I recognized that further study would be required on this issue during Phase III.
- 23. As I discussed above, at the time I became Head of the Anti-Infective Venture, I was aware the FDA had raised general concerns regarding QT prolongation issues regarding all antibiotics, including macrolides and ketolides. I had noted that this general FDA concern was reflected in some of the documents I had reviewed. For example, the ABT-773 Update dated February 12, 2001 that Dr. Sun had provided to me in February, noted that "[t]he potential for QT prolongation is currently a prominent issue facing drug development across therapeutic areas-worldwide." D's Exhibit 608 at ABBT205042. There was thus an external environment in which QT prolongation was a general regulatory concern at the time for all drugs, not specifically for ABT-773. I was aware of, and the team discussed the fact that QT prolongation was a general drug safety issue

that needed to be studied in preclinical and clinical trials for antibiotics and, more generally, all pharmaceutical compounds. I was also aware that Abbott would need to provide sufficient data to the FDA to establish the safety of ABT-773 with regard to QT prolongation and to continue to monitor ABT-773 for QT prolongation. In other words, as with all drugs, there was an expectation that we would have to do due diligence, including further studies, to show the FDA that there were no disqualifying safety issues, including QT prolongation problems, with ABT-773.

24. At the time I became Head of the Anti-Infective Venture in April 2001, based on the information provided to me by the responsible ABT-773 team members and by Dr. Sun, I understood that no significant QT issue had been identified for ABT-773 that raised a concern for the future of the compound, despite my understanding that some data indicated that QT prolongation had been experienced with superphysiological doses of ABT-773, doses that far exceeded the therapeutic doses that Abbott was considering for the compound. As set forth in the ABT-773 Update Presentation of February 12, 2001, "no consistent QT effect was observed at clinical doses studied in the Phase IIb studies." D's Exhibit 608 at ABBT205061. Similarly, an ABT-773 update presentation prepared by the ABT-773 program, dated March 19, 2001, which I reviewed in the ordinary course of business at or around the time I became head of the program, summarized Abbott's knowledge of the QT prolongation question as it applied to humans as follows: "Possible dose effect in Phase I at daily dose > 800 mg; No significant QT effect in ketoconazole interaction study; No clinically relevant QT effect in Phase III studies 150 -- 600 mg daily...." Attached hereto as D's Exhibit 631 is a true and correct copy of this March 19, 2001 update presentation (see p. ABBT120480). In sum, I was not aware of any

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evidence as of the time I became venture head in April 2001 that the FDA had any reason to believe that it should have a specific concern about ABT-773 or that Abbott had such a concern. Nor did I believe that anything related to QT prolongation would even delay, much less prevent, the successful launch of ABT-773.

- 25. Based on my experience in the industry and the information provided to me by my colleagues, I was aware when I became venture head that such successful macrolide antibiotics as clarithromycin had a QT prolongation effect, but this effect was within generally acceptable parameters for an antibiotic used for community-acquired diseases. Accordingly, even if ABT-773 had experienced QT issues, that would not have led me to believe that ABT-773 could not win regulatory approval or experience commercial success. Rather, I understood that ABT-773 would need to demonstrate a safety profile with respect to QT prolongation similar to clarithromycin, assuming at least a similar efficacy profile.
- 26. In or around April 2001, I was aware as a result of my review of documents and discussions with Abbott employees that the FDA had previously asked Abbott in December 2000 to undertake a two-week dog toxicology study focused on QT and liver toxicity issues. Based on discussions with Abbott's Regulatory Affairs group, it is not unusual for the FDA to call for a variety of incremental studies, particularly preclinical studies such as this dog toxicology study, as the FDA begins to evaluate the data presented to it. I did not regard the request for the dog toxicology study as either unusual or as raising any significant concern for the development of ABT-773. My view of the request for the additional dog study proved correct: By May 2001 the ABT-773 program was able to report to senior management in the program's monthly status report at

ABBT0000510 that this "[a]cute tox study in dog showed no difference from the earlier sedated dog study," which had had satisfactory results. Attached hereto as D's Exhibit 638 is a true and correct copy of the May 2001 monthly status report.

- 27. I was aware in or around April 2001 that members of the scientific community and the pharmaceutical industry were engaged in a vigorous debate about the best ways to read and accumulate QT prolongation data and that new technology was beginning to allow such data to be collected electronically, eliminating certain human errors.
- 28. At my direction and under my supervision, the ABT-773 program undertook two major efforts to confirm the quality of the assessment of the QT prolongation data and the program's conclusion that QT prolongation was not an issue for ABT-773. First, the program re-read every single ECG collected in the entire ABT-773 program, using the best available method and under the supervision of a leading expert in the field. Second, Abbott conducted a large, very rigorous clinical trial in which thousands of ECGs were collected using the best available technology. These two efforts confirmed that there was no QT prolongation signal for ABT-773 significant enough to impede regulatory approval.
- 29. Abbott continued to study the potential for QT and liver toxicity issues, along with many other issues, during the ABT-773 clinical program that went forward after I became Head of the Ant-Infective Venture. These issues, along with all of the other issues that face drug development compounds, continue to be evaluated until the drug is submitted for approval. As I discussed above, however, I did not have any significant concerns that any QT or liver toxicity questions would negatively affect the development of the compound.

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ABT-773: Status of Dosing Decisions (QD or BID) For Four Indications as of April 2001

- 30. When I became Head of the Anti-Infective Venture in April 2001, I was aware that the ABT-773 adult oral formulation program was working to determine the proper dosing, QD (once-a-day) or BID (twice-a-day) for ABECB, pharyngitis, CAP, and ABS, the four indications for which adult oral formulation of ABT-773 was being developed. I was also aware from my review of documents and my discussions with ABT-773 team members that the most valuable market for ABT-773 was in the two less severe indications, ABECB and pharyngitis, which account for approximately 80% of the global respiratory anti-infective market. I recognized that that Abbott's commercial group, in line with market trends, would prefer to have all indications at QD dosing. However, I did not believe that twice-a-day ("BID") dosing for the more severe indications would prove a significant commercial challenge because many of the drugs on the market for those indications were twice-a-day (BID) or three-times-a-day ("TID"). Moreover, although I understood that the commercial team believed once-a-day dosing was preferable (though not an absolute requirement) for the US market, based on my experience in the industry and the information made available to me by the ABT-773 team, I also understood it was less of an issue in markets outside the United States, which were expected to account for a little less than half of the total sales of ABT-773. In fact, I understood that in some parts of the world, such as Japan, it might be seen as preferable to have a more frequent dosing.
- 31. In or around the time I became venture head in April 2001, I understood from reviewing ABT-773 data and my discussions with responsible members of the ABT-773 team, that we expected that the dosing for the two less severe indications, ABECB and

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32. I reached my understanding of the ABT-773 dosing issues in or around April 2001 from, for example, the Abbott documents that were provided to me in that time frame and which I reviewed at that time. Thus, Abbott's December 5, 2000 portfolio review indicates that as of December 2000, Abbott's Phase II clinical data supported once-a-day dosing for the two less severe (and more commercially significant) indications and the possibility of either once-a-day or twice a day dosing for the two more severe indications. D's Exhibit 608 at ABBT205114. Similarly, the ABT-773 Update dated February 12, 2001 states that "Phase II ABECB and pharyngitis/tonsillitis data supported 150 mg QD," that "150 mg QD currently being evaluated in ongoing Phase III trials in these indications," that additional dose ranging trials were ongoing for CAP and sinusitis, since there was as yet insufficient data to make a dosing decision as to those indications, and that "[a] decision of 150 mg 'QD vs 150 mg BID in CAP & sinusitis will be made based on phase III date 2Q01." D's Exhibit 608 at ABBT205069-70. Abbott's March 2001 internal monthly status project report for ABT-773 also

projects a "High" probability of achieving once a day dosing for the two less severe indications. D's Exhibit 613 at ABBT0000429.

<u>ABT-773:</u> Status of Pediatric Program as of April 2001 and Plans for Further Development in Following Months

- 33. Based on the information provided to me by Dr. Sun and members of the ABT-773 team and on the data I reviewed when I became venture head, I understood in and around the time I became Head of the Anti-Infective Venture that the ABT-773 pediatric oral suspension program was on hold, but that a prototype formulation had been created, certain studies had been completed, and others were planned. This work was reported in the ABT-773 Portfolio Review presentation dated December 5, 2000, which Dr. Sun provided to me in February 2001, and which I reviewed at the time. D's Exhibit 608 at ABBT205236-205248. In the ABT-773 Update of February 12, 2001, which Dr. Sun also provided to me in February 2001, and which I also reviewed at that time, the program reported that the "[t]he first prototype [pediatric formulation] tested had a taste that was better than clarithromycin," although "not as good as azithromycin," and that, while the pediatric program was currently "on hold," Abbott planned in the future to "reevaluate possible ways of overcoming the taste problem." D's Exhibit 608 at ABBT205046. Thus, based on this information and discussion I had with team members in and around the time I became venture head, I understood in April 2001 that, although there were taste issues with regard to the bitterness of the formulation, the program would be moving forward under my direction by doing further work on the pediatric formulation.
- 34. Although the pediatric program was temporarily on hold and not funded for calendar year 2001, I and the ABT-773 program team did not consider this situation a

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matter of concern. Under my supervision, in May 2001 the ABT-773 team completed an assessment of the pediatric development to date and developed a proposal to move forward with further formulation development and Phase I studies, with a view toward finalizing this proposal by July 31, 2001 and presenting it to senior management. D's Exhibit 638 at ABBT0000509 notes this effort. As discussed above, it was my custom and practice in the ordinary course of business as Head of the Anti-Infective Venture to review and approve this monthly status report before it was finalized. This ABT-773 team proposal regarding the pediatric formulation, as well as the fact that Abbott projected spending \$9 million on the ABT-773 pediatric program in 2002 and \$21.5 million in 2003, was in fact discussed at a ABT-773 Decision Analysis Core Team meeting on or around July 25, 2001, which, as I recall, I attended. I also participated in preparing and reviewed and approved the accuracy of the presentation that was made at this meeting, a true and correct copy of which is attached hereto as D's Exhibit FT (see especially pp. ABBT103235.UR - ABBT103239.UR and ABBT103224.UR). Consistent with this Decision Group Analysis and the plans the program had developed under my supervision for the pediatric formulation, in the July 2001 ABT-773 Monthly Status Report, the program reported to senior management that "[a]n assessment of the Pediatric program to-date was completed, and a proposal to move forward with further formulation development and Phase I studies has been developed. FDA guidelines for a pediatric formulation require companies to show due diligence with a pediatric development program. A pediatric proposal will be made to senior management." Consistent with my custom and practice, as discussed above, I would have reviewed and approved this monthly status report in the ordinary course of business before it was finalized. Attached

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35. During the time that I was Head of the Anti-Infective Venture, I was not concerned that the status of the pediatric program would prevent or delay the launch of ABT-773. Based on my discussions with Abbott's Regulatory Affairs team, I understood that the FDA required only that Abbott be conducting pediatric studies at some time prior to regulatory approval of the adult formulation. It was my further understanding Abbott would not be prejudiced in its ability to obtain FDA approval of an adult formulation if its pediatric program was not completed at the time it sought that approval. Moreover, based on my experience in the industry, it is my understanding that the ABT-773 program's planned timing for the development of the pediatric formulation after that of the adult formulation was not at all unusual, given the fact that it is generally considered unacceptable to test products in children until after the products have demonstrated an acceptable level of safety in adults.

The Impact of the FDA's Ketek Advisory on the ABT-773 Program

The regulatory hurdle with regard to ABT-773 changed dramatically in late April 36. 2001. On April 26, 2001, the FDA held its first advisory committee meeting for Ketek, a ketolide that was under development by another pharmaceutical company, Aventis, and

was at a more advanced stage of development than any other ketolide. I watched this Ketek advisory together with members of the ABT-773 development team via satellite at Abbott Park. At this meeting, the FDA Advisory Committee voted against approval of Ketek for AECB and ABS, did not address pharyngitis, and stated that Ketek needed additional data on QT prolongation and liver toxicity prior to approval for CAP. Attached hereto as D's Exhibit AC is a true and correct copy of an April 27, 2001 email from Jeanne Fox to me, and others, forwarding an April 27, 2001 Health News Daily Article regarding the Ketek Advisory.

- 37. The April 26, 2001 Ketek advisory was unexpected in a variety of ways. First, prior to the advisory, we believed that Ketek would receive regulatory approval. In the ABT-773 Portfolio Review presentation dated December 5, 2000, which Dr. Sun provided to me in February 2001, the program stated "Ketek . . . will be first-to-market ketolide . . . FDA advisory 1/29. . . Expected approval 1Q01." D's Exhibit 608 at ABBT205118 (emphasis in original).
- 38. The second unexpected (and even more important) aspect of the Ketek advisory related to the focus of the Advisory Committee's concerns. Based on the information that had been provided to me before and shortly after the time I became venture head, I understood from information provided to me by the ABT-773 team that Abbott had expected the focus of the Ketek advisory to be "related to concerns about efficacy and not related to QTc concerns," as discussed in the ABT-773 Update February 12, 2001 that had been provided to me by Dr. Sun in February 2001. D's Exhibit 608 at ABBT205043. In fact, however, the Ketek advisory focused both on efficacy and on the size of Ketek's

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safety database, as the April 27, 2001 Health News Daily Article attached to Jeanne Fox's April 27, 2001 email made clear. D's Exhibit AC.

- 39. Prior to the Ketek advisory, there was no clear direction as to the required size of the safety database for community antibiotics, but based on prior experience it was thought to be about 4,000 patients exposed to the drug. It was also unclear what number of isolates would be necessary to establish a resistance claim, an issue which also directly implicated the size of clinical trials. For example, in the January 2001 MPSR, the ABT-773 program stated that "FDA feedback" regarding a resistance claim was only that a undefined "sufficient body of evidence" needed to be gathered to convince the FDA to grant a claim, and that "they estimate >10 resistance isolates will be required". Attached hereto as D's Exhibit 587 is a true and correct copy of that document. On the basis of our knowledge about the regulatory requirements prior to the Ketek advisory, the program under my supervision, planned for a safety database for its QD testing of 4200 patients, a CAP database (for the resistance claim) of 1000 patients, and estimated 17 isolates. Based on all the information available to us prior to the Ketek advisory, we assumed these plans would be sufficient. This assumption was incorrect, as was shown by the Ketek advisory.
- 40. The Ketek advisory "raised the bar" for the development of ABT-773 significantly by making it clear that the FDA would in the future require more isolates and therefore greatly increased numbers of patients in clinical trials to prove up a resistance claim, if the claim was achievable at all. Moreover, although it had been known before the Ketek advisory that the FDA was very interested in QT prolongation issues with regard to antibiotics, the fact that Ketek, the first in class drug under review,

was deemed to have issues placed an additional burden on all other drugs in the class being reviewed, including ABT-773, with regard to demonstrating safety. It was only with the Ketek advisory that it became apparent how much the FDA would focus on QT prolongation and what type of evidence would be required. For this reason further data would be required, even if, as was the case with ABT-773, there was no existing evidence indicating that the compound itself had QT issues. With regard to liver toxicity, the impact on Abbott and other drug companies of the Ketek advisory was similarly dramatic. For example, the Ketek advisory revealed that Aventis would be required to perform a 20,000 patient study for liver toxicity because of only two specific cases of liver toxicity that had occurred in the Ketek database. This newly expanded study was expected to cost Aventis tens of millions of dollars and last several years.

41. In the wake of the Ketek advisory, the ABT-773 team, under my direction and supervision, analyzed its implications for us and made presentations to senior management setting forth our conclusions. I contributed to the preparation of some of the slides used in these presentations, and reviewed and concurred with the information set forth in the presentations as a whole. I participated in the actual presentations made to senior management of these materials. For example, attached hereto as D's Exhibit 649 is a true and correct copy of an email from Carol Meyer to me and others dated June 20, 2001, attaching one iteration of such a presentation. Reflecting the ABT-773 program's conclusion as to the importance of the Ketek advisory, the "headline" for the slide beginning the discussion of the Ketek advisory in this presentation is "The Ketek advisory raised the hurdle for the approval of ketolides," and the slide goes on to note that the FDA advisory committee had found "Ketek's 3700 patient safety database

insufficient". The slide also notes that the FDA had found the number and cure rates for Ketek's resistance claim isolates insufficient. *Id.* at ABBT229437. The next slide in this presentation spells out the implications that the Ketek advisory had for Abbott's safety database. Specifically, for the QD outcome, this presentation estimated that the safety database needed to be increased from 4200 to 5000, the CAP patients from 1000 to 1500, and the estimated number of resistance isolates from 17 to 25. Each of these increases, as well as those for the BID outcome databases, meant many millions of dollars in increased costs for the program. An ABT-773 Decision Analysis Core Team presentation, dated July 23, 2001, which I also helped prepare and present on July 25, 2001, sets forth similar conclusions as to the importance and impact of the Ketek advisory, stating that the "Ketek advisory defined new regulatory standards," and "influences program size". D's Exhibit FT.

- 42. D's Exhibit 614 is a December 2001 ABT-773 presentation to senior management reflects that after further analysis of the Ketek advisory we had concluded that we would have to add still more patients to the safety database, requiring greater additional expenditures and even more time than we had originally calculated. Attached hereto as D's Exhibit 614 is a true and correct copy of the December 2001 "ABT-773 Agenda" presentation (see pp. ABBT271786-87).
- 43. In sum, the information we had received from the Ketek advisory, and our analysis of its implications, led us to conclude that the Ketek advisory was a watershed for the ABT-773 program, not because of any specific concerns about ABT-773 itself, but because of the increased stringency of the regulatory environment, likely for all antibiotics but for ketolides in particular. This increased stringency, only made apparent

by the Ketek advisory, meant that Abbott would have to re-think the size and adequacy of our safety database and evidence and also the number of isolates that would be required to establish a resistance claim. I and others at Abbott concluded that the Ketek advisory meant that the ABT-773 program would have to incur much greater expense and take much longer to complete than we had had anticipated prior to April 26, 2001 if we hoped to satisfy the FDA's requirements. These conclusions are reflected in summary of the status of ABT-773 in an "Operations Highlights" presentation for a September 7, 2001 Board of Directors meeting. Attached hereto as D's Exhibit 501 is a true and correct copy of this presentation. Specifically, this presentation states, "Based upon experience gained from . . . Ketek FDA advisory meeting, the size of ABT-773 (Ketolide antibiotic) safety database has been increased. This will result in a one year delay in the filing of ABT-773." I provided input to this portion of the presentation and agree with its contents, based on my experience and knowledge of the ABT-773 program at the time.

Post-Ketek Advisory Events Negatively Affecting the ABT-773 Program

44. As discussed above, as of March and April 2001, we were evaluating whether to continue to pursue once-a-day dosing for the two more severe indications, CAP and sinusitis, or pursue twice-a-day dosing. We were planning to base this decision on our analysis of the clinical data that would be released in the summer of 2001. By July 2001, after we had analyzed the Ketek advisory, the clinical data was not yet available, and we faced the decision of whether to wait for the release and analysis of the data, and lose time on the path to regulatory approval, which we now believed in light of Ketek would in any event take longer than we had previously estimated, or make a decision based on the available data. In order to minimize risk and avoid delays on the path to regulatory

approval, we decided to pursue twice-a-day dosing for the launch of CAP and sinusitis. This decision is reflected in D's Exhibit FT, the July 23, 2001 ABT-773 Decision Analysis Core Team presentation discussed above, at ABBT103208.UR, where the presentation notes that the "expected value of selecting the BID dosing" for CAP and sinusitis exceeded the "value of waiting for the dose-ranging data" from clinical studies that were still ongoing. This was not an irrevocable decision, however. As reflected in the ABT-773 July 2001 status report, we planned to continue to evaluate options to achieve once-a-day dosing for those indications, and to attempt to develop an effective once-a-day dose for them after the initial launch. D's Exhibit 654 at ABBT0000589. In addition, we continued to plan a program by which we would be able to offer once-a-day dosing for the less severe indications. *Id*.

Document 362-2

45. In November 2001, the results of a critical pharyngitis trial indicated that ABT-773 at the QD 150mg dose would not demonstrate sufficient efficacy for that indication. The loss of this indication, one of the larger indications for which ABT-773 adult oral formulation was being developed, had extremely negative implications for the potential value of ABT-773. In a January 7, 2002 memorandum regarding the status of ABT-773 that Dr. Sun and I prepared based on information for ABT-773 team members and sent to Miles White, Abbott's CEO, we stated that "[t]he loss of the pharyngitis indication is forecasted to erode more than \$117 million in NPV from ABT-773 " Attached hereto as D's Exhibit 673 is a true and correct copy of this memorandum (see pg. ABBT207775). In the presentation to Mr. White regarding ABT-773 that I prepared and made in January 2002, a true and correct copy of which is attached hereto as D's Exhibit 676, I similarly emphasized the negative impact on the program resulting from the failure

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of the pharyngitis indication. *Id.* at ABBT220672 (indicating a loss of \$117 million due to pharyngitis) and ABBT220666 ("By losing the pharyngitis indication, ABT-773 is left to compete in 53% of the adult global respiratory anti-infective market."). To the best of my knowledge, based on my knowledge of and experience with ABT-773, the information included in the January 2002 memorandum and presentation was true and accurate. I understood at the time I participated in the preparation of these documents that they would be relied upon by Abbott's senior management in making decisions about the ABT-773 program.

46. As I set forth in the above-referenced January 2002 presentation and memorandum to Mr. White, there were several events that had occurred after April 2001 that had a profound negative impact on the ABT-773 program and caused the members of the ABT-773 to have much greater concern about the future of ABT-773 than the team and Abbott generally had had prior to April 2001. First, as I explained in the January 7, 2002 memorandum to Mr. White, the Ketek advisory demonstrated an environment of "[i]ncreasing regulatory stringency" and meant that "the projected size of the required safety database for ABT-773 has increased considerably [as a result of the Ketek advisory]. This will increase the expense and duration of the phase III trials." D's Exhibit 673 at ABBT207774. Second, I noted that the Ketek advisory made clear that a resistance claim for ABT-773 would require a "larger number of resistant isolates" and that, like the need for a larger safety database also established by the Ketek advisory, "this requirement will significantly increase the size, complexity, and duration of clinical trials". *Id.* Third, I emphasized that "the loss of the pharyngitis indication (as demonstrated by late 2001 clinical trial results) is forecasted to erode more than \$117

MM in NPV from ABT-773." *Id.* at ABBT207775. Fourth, I explained that in July 2001 the program had determined, in light of the increasingly stringent regulatory environment evidenced by the Ketek advisory and other information developed since April 2001, had chosen "twice daily dosing . . . for the pivotal Phase III clinical trials in sinusitis and community acquired pneumonia. This decision was taken based on accumulated scientific data and to enhance regulatory approvability of the compound, but recognizing a corresponding decrease in the commercial value. . . . " *Id.* at ABBT207773. Fifth, I noted that "liver enzyme elevations had been observed in a few subjects in clinical trials, most recently in a study to evaluate QT prolongation." Id. at 207775. The recent trial to which we referred in this memorandum was the Abbott M01-325 clinical trial, which began on October 3, 2001, and which was put on hold due to unexpected liver elevations seen in four patients. As we stated in the January 2002 memorandum to Mr. White, "Although the incidence and severity of these findings fall within an acceptable range for antibiotics, further findings may drive the requirement for a larger safety database". Id. In other words, we were concerned, after the Ketek advisory, that any clinical trial safety data that implicated safety concerns, even if that data was within an acceptable range for antibiotics, could result in an FDA requirement of a greatly enlarged safety database and cause Abbott to incur much greater development costs than it had expected prior to April 26, 2001, to prove that ABT-773 was safe. The safety issues referenced in the January memorandum to Mr. White were significant only in light of the fact that April 2001 Ketek advisory had significantly raised the hurdle for establishing safety for the class of drug to which ABT-773 belonged. D's Exhibit 676 at ABBT220671 ("Complete analysis of liver function tests of entire database revealed no significant case of liver toxicity.

However, a finding of a single case in the future could drive database requirement of up to 10,000 patients.").

47. In slide 1 of the January 2002 presentation, which I gave to Mr. White, I summarized the most important information that we had learned about ABT-773 since before the Ketek advisory in April 2001 as follows:

> Since the April PEC, the development plan has been impacted by:

> The Ketek (Aventis) advisory defined the minimum safety and resistance databases for Ketolide anti-infectives

> The BID dosing at variance with market trend to short course once daily therapy

> Loss of pharyngitis indication impacts program financially and has regulatory impact

> The drug is still technically approvable with cost and time penalties, but commercial attractiveness has decreased substantially.

D's Exhibit 676 at ABBT220665.

Each of these issues was based on developments that occurred after March 2001, when I understood the agreement between Hancock and Abbott was entered into.

Abbott's December 10, 2001 Decision to Place the ABT-773 Program on Hold and Mid-2002 Decision to Terminate Development of ABT-773 and Out License the Compound

48. On December 10, 2001, the PEC met to review the development status of ABT-773. At that meeting, I presented the information that the program had received about ABT-773 and the regulatory environment since mid-April 2001. Based on the data it reviewed at that meeting, the PEC put the ABT-773 program on hold, although existing studies were to be completed. In addition, as set forth in the January 7, 2002 memorandum from Dr. Sun and myself discussed in detail above, the PEC also

recommended to Mr. White that Abbott suspend further development of ABT-773 and initiate efforts to out license the compound. D's Exhibit 673 at ABBT207773.

- 49. I attended a meeting with Mr. White in January 2002 in which I made a presentation setting forth the basis for the PEC's recommendation to suspend further development. Mr. White did not announce any decision about the future of ABT-773 at that time. We completed the existing clinical studies through the first half of 2002. However, no new studies were started. In February 2002, we informed our employees that there was a delay in the development timeline of ABT-773. Towards the middle of 2002, Dr. John Leonard informed me to fully suspend development of ABT-773 and work with the licensing group to explore the out licensing of the compound.
- Abbott's Out Licensing of ABT-773 to ALS
- 50. I was actively involved in Abbott's efforts to out-license ABT-773 after the decision had been made that Abbott would discontinue its development of the compound. I participated in presentations that Abbott made to potential partners, including Elitra. I was aware that Abbott negotiated a license agreement with Elitra in December 2002. I was also aware that Elitra's funding fell through after several months and it was unable to develop ABT-773. I also participated in meetings with Advanced Life Sciences ("ALS").
- 51. After Hancock had given its consent, Abbott entered into an ABT-773 licensing agreement with ALS in December 2004. I participated regularly in discussions with ALS regarding the development of the compound and I monitored that development. When I began my work with Astellas, Astellas asked me to discontinue my work with ALS. I continue to monitor the development of the compound through the public announcements

that ALS occasionally makes about it and through information that ALS sends me from time-to-time.

ALS's Development of ABT-773 ("Cethromycin")

- 52. Based on my participation with regard to ABT-773 on the ALS scientific board review and my review of publicly available sources, I am aware that ABT-773 is currently under development as "cethromycin" by ALS. On June 21, 2007, ALS announced results from its most recent clinical trial. Attached hereto as D's Exhibit 732 is a true and correct copy of the June 25, 2007 Advanced Life Sciences Form 8-K. According to ALS, ABT-773 or cethromycin "achieved positive safety results in the study" and "liver function tests and electrocardiogram monitoring demonstrated no significant differences between subjects receiving cethromycin and subjects receiving Biaxin," an antibiotic that is currently on the market today. *Id*.
- 53. Based on my review of publicly available sources, I am also aware that ALS has publicly announced that: (1) it expects to launch the drug to the public at the end of 2008; (2) it plans to launch with once-a-day dosing; (3) the drug's safety profile is consistent with Biaxin, an antibiotic currently on the market; (4) analysts have projected that the compound could achieve peak sales of \$500 million a year; and (5) under the terms of the RFA and the out-licensing agreement that Abbott negotiated, with Hancock's approval, Hancock will receive substantial royalties and milestone payments if ALS successfully launches the drug. See, for example, June 25, 2007 Advanced Life Sciences Form 8-K; Crain's Chicago Business June 29, 2007 Article ("According to Elmer Piros, a New York-based analyst with Rodman & Renshaw LLC, Cethromycin could eventually reach 25 percent of the \$2-billion global market for drugs that fight community-acquired

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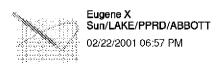
Filed 03/10/2008

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pneumonia."); Crain's Chicago Business June 11, 2007 Article ("If the drug passes its trial, analysts expect FDA approval and a product launch by year-end 2008."); and Life Sciences Weekly August 21, 2007 Article (ALS "announces positive results" from key cethromycin clinical trial"), true and correct copies of which are attached hereto as D's Exhibit 732, BU, BS and BX, respectively.

STANLEY BUKOFZER, M.B., B.Ch., M. Med. (Int. Med.)

EXHIBIT 608 Part 1



To Stan Bukofzer/LAKE/AI/ABBOTT@ABBOTT cc

bcc

Subject 773 material

Stan,

here are some background materials



ABT-773 Development Plan 1.doc



Leiden review Dec00.ppt



End of Phase 2 Meeting Minutes.doc



End of Phase 2 Meeting - Primary Slides.ppt



ABT773 Review Pharma Exe Meeting.rtf



ABT-773 Pharma Exe Meeting.ppt

Confidential ABBT204959

ABT-773 DEVELOPMENT PLAN C. Meyer [DATE]

Confidential ABBT204960

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A. Executive Summary

SWOT Analysis A.1

7	Fable A.1 SWOT Analysis (Strengths/Weakness	es/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY		
Strengths	ABT-773 is active against penicillin-resistant and macrolide-resistant <i>S. pneumoniae</i> including Erm AM and Mef phenotypes; it has not been shown to induce MLS _b (macrolides, lincosamides and streptogramin B) resistance.	Key positioning in the marketplace as a safe, effective antibiotic that treats resistant organisms and does not induce resistance. Capitalize on micro superiority and lower		
	The in vitro microbiological profile of ABT- 773 shows a 4-fold superiority to telithromycin which should translate into 3 to 5 times lower daily dose than the first ketolide.	dose by generating comparative efficacy/safety data in Phase IIIb studies.		
Weaknesses	Pharmacokinetic profile does not meet the preconceived ideas of some PK/PD experts. Because of this, the 150mg QD dose may be challenged. In Phase IIb studies, 300 mg QD has higher	Phase IIb studies indicated efficacy with 150 mg daily dose in ABECB and ABS. PK/PD data together with ribosome kinetics support the decision to proceed with 150mg QD in mild infections (ABECB and ASP) and select between 150mg BID and 150mg		
	GI/Taste perversion adverse events compared to clari 500 mg BID	QD in CAP and ABS. Recent PK/PD data support AUC of 1-6 for clinical exposure in		
	The Phase III clinical program is large, intense, and must be conducted successfully in a relatively short period of time. There is also very stiff competition from other major pharmaceutical companies to enroll patients. Many of these companies are paying inflated grants fees and have simpler Phase IV protocols that will entice investigators.	CAP necessary for cure. Monitor enrollment closely and be proactive with CROs in opening additional sites and offering appropriate incentives to push enrollment. Prepare to open sites in the Southern hemisphere.		
An IV and pediatric formulation will not be available at launch. An IV formulation we further enable us to position this product as effective drug for a range of mild to severe infections. A pediatric formulation would further underscore the safety properties of a product. Both formulations would promote improved acceptance of this product.		HPD has identified initial funding this year to bring an IV prototype into Phase I studies. Further development funding has been requested in 2001 in the IIPD plan and has been included in a PPD blue plan request. Present initial pediatric Phase I data as well		
		as taste evaluation will be available mid- October for management decision on future funding.		
Opportunities	ABT-773 has the potential to be able to address competition with azithromycin with short course therapy for mild infections, as well as quinolones for more serious infections. Resistance (PRSP/MRSP) is a growing concern and will be a major consideration when this product is introduced.	Conduct appropriate comparative Phase III studies to get approval for all the RTI indications, both in U.S. and European countries. Collect enough resistant isolates to obtain the claim for resistant S. pneumoniae.		

		· ·
	If 150mg QD is proven effective, COGs for this product will be within a very acceptable range for obtaining a high profit margin in all markets. Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i> .	Continue to improve throughput and yield and introduce appropriate process improvements in SPD to further bring down the bulk drug costs. Propose intermediate step 5 as the starting material for the bulk drug to enable further process improvements post-filing. This opportunity exists for the FDA labeling only and recent information indicates that FDA is rethinking their position on granting this separate claim. Other antibiotics have been granted this claim with as little as 15 isolates.
Threats	Current data available is insufficient to predict that 150mg QD will be effective in more serious indications of CAP and Sinusitis. Current two dose studies are being carried out in 150mg QD and 150mg BID to assess the potential of 150mg BID being the required dose for these indications.	May need to market 150mg QD for mild infections and 150mg BID for more severe infections.
	Regulatory uncertainties over how to deal with ketolide/macrolide class	ABT-773 is similar to clarithromycin and erythromycin in its effect on QT intervals in preclinical studies Current clinical data indicates no evidence of QTc prolongation. ECG monitoring is included in all the Phase III studies. An HPD funded phase I study of an IV formulation prototype will provide additional information on QTc prolongation.
	Elevated liver enzymes were seen in a small number of Japanese volunteers in a PK study.	Current expert analysis has concluded that there no clinically significant interaction. The study is being repeated in Japan to further evaluate.
	The Japanese development program has been delayed due to findings in the first Japanese PK study indicating a significant difference in the PK profiles between Japanese and non-Japanese subjects. Timing, dose selection and funding for the Japanese program is unknown at this time.	Repeat Japanese PK study in Japan along with a food effect study. Once results are available, meet with clinical advisory committee KIKO and determine the development requirements for Japan.

A.2 Development Plan Summary

Considering the rapid and extensive emergence of penicillin and macrolide resistant *S. pneumoniae*, and the remaining patent life of Clarithromycin, the flagship of Abbott's pharmaceutical product line, ABT-773 was approved by PPCC in 03/97 as a candidate for Development by the Anti-Infective Venture. The mission of the Venture is to develop ABT-773

as a first line therapy in community acquired lower and upper respiratory infections (RTIs).

The proposed indications and treatment durations below position this product to compete effectively in the RTI arena both in the U.S. and in international markets. These are the required indications to be considered as first line therapy for RTIs.

٠	Community-Acquired Pneumonia	10 Days
•	Acute Bacterial Sinusitis	10 Days
•	Acute Bacterial Exacerbation of Chronic Bronchitis	5 Days
•	Acute Streptococcal Pharyngitis/Tonsillitis	5 Days

Our goal is to provide the physician with an agent which will have the safety and tolerability of azithromycin for mild to moderate infections but with the strengths of the quinolones for moderate to severe infection of the respiratory tract particularly for (PRSP/MSRP) resistant *S. pneumoniae*.

We will also be seeking additional labeling to include the treatment of macrolide-resistant Streptococcus pneumoniae, penicillin-resistant Streptococcus pneumoniae, and atypical pathogens to include C. pneumoniae, M. pneumoniae and L. pneumophila in the above-mentioned indications. Susceptibility and clinical treatment trial data for macrolide-resistant Streptococcus pneumoniae and penicillin-resistant Streptococcus pneumoniae will be provided from Phase 3 trials. A request for appropriate breakpoints to include these strains will also be provided in the NDA.

B. Marketplace

Marketplace SWOT Analysis **B.1**

Table B.1a SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)							
CATEGORY	ITEM (Probability/Impact)	STRATEGY					
	Large market in terms of both prescriptions and sales	None					
Strengths	Emerging international markets may contribute to positive market growth ex-U.S.	Move forward with global development program					
	Antibiotic resistance ultimately renders older agents obsolete, allowing newer agents access to the market	Target resistance claim for ABT-773					
	May be negative pressure on antibiotic usage stemming from increasing antibiotic resistance	Monitor appropriate use guidelines and their impact on antibiotic usage; where possible, attempt to influence decision making bodies (FDA, CDC, NCCLS)					
Weaknesses	Difficult to differentiate antibiotics	Leverage product strengths (targeted RTI spectrum, activity, ribosome binding) to create a differentiation strategy					
	High hurdle rate for new agents in terms of convenience and adverse event profile	Evaluate ABT-773 profile upon receipt of phase III data					
	High level of promotional support required to reach optimal sales levels	Build adequate promo levels into LRP					
	ABT-773 represents a hedge against Biaxin IR patent expiration in 2005	Evaluate optimal portfolio/promo strategy between Biaxin XL and 773 in light of patent expiration					
Opportunities	Potential for I.V. formulation, expands scope of franchise into new market segment	Continued funding of IV program					
	Potential for pediatric formulation	Make go/no-go decision based on taste/PK data					
	Telithromycin launch 2-1/2 years in advance of ABT-773	Monitor launch of telithromycin, adjust 773 strategy if necessary based on market feedback					
	Considerable number of antibiotics lose patent exclusivity by 2005-may put negative price pressure on market	Work with managed care group to evaluate potential impact					
Threats	May be negative pressure on antibiotic usage stemming from increasing antibiotic resistance	Monitor appropriate use guidelines and their impact on antibiotic usage; where possible, attempt to influence decision making bodies (FDA, CDC, NCCLS)					
	New entrants	Leverage product strengths (targeted RTI spectrum, activity, ribosome binding) to create a differentiation strategy					

Filed 03/10/2008

B.2 Epidemiology/Disease Class

Respiratory tract infections represent the majority of community-acquired infections. Causative pathogens for these infections are most often Strep. pneumoniae, H. influenzae, M. catarrhalis, and M. pneumoniae. Table X summarizes the annual incidence of community-acquired respiratory infections.

Table B.2.1: Annual Incidence of Community-Acquired Infections

	Infection	Annual Incidence	Annual Incidence				
		(U.S., millions)	(Ex-U.S., millions)				
Upper Respiratory	Sinusitis	37	94				
	Otitis	18	46				
	Pharyngitis	12	30				
Lower Respiratory	Bronchitis	14	36				
	Pneumonia	4	10				

B.3 Market Overview

U.S. Market

1999 U.S. antibiotic prescription and sales data are presented in the table below.

			1995	1996	1997	1998	1999	CAGR95.99
	TRXs (MM)	Tab/Cap	220	215	211	208	221	0.1%
i		Oral Susp.	76	66	63	59	61	-5.3%
20)]	I.V.	NA	NA	NA	NA	NA	NA
∹	8 S	Tab/Cap	\$4,057	\$4,220	\$4,467	\$4,848	\$5,715	8.9%
	Sales (\$MM	Oral Susp.	\$1,075	S979	\$977	\$1,001	\$1,120	1.0%
	~ · · · ·	I.V.	\$1,865	\$1,829	\$1,855	\$1,890	\$2,117	3.2%

Tab/cap and oral suspension prescriptions had been declining 1-2% per year in the period of 1995-1998, presumably from increased attention to appropriate prescribing in the face of increasing resistance; however, prescriptions recovered in 1999, though this may be explained at least in part by a relatively late 1998-99 flu season. Even in the face of this negative pressure on antibiotic use, however, sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics; during 1995-1999, generic tab/cap prescriptions declined by 30MM. So while negative pressure on the use of these antibiotics continues, it appears the market is willing to bear higher costs for agents that meet unmet need. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

The macrolide class has grown significantly over recent years, from \$771MM in 1995 to \$1,596MM in 1999, though most of this growth (S673MM) was due to gains in Zithromax, underscoring the importance of convenience, adverse event profile, and price in this market.

Filed 03/10/2008

Ex-U.S. Market

The ex-US antibiotic market had sales of \$11.6B in 1999, an increase of approximately 5.9% over 1998; however the CAGR over the past 3 years has been only 0.7%. Antibiotic usage is expected to decline 1-2% per year in the largest, most developed AI regions – Europe, Japan and Canada; however, Latin America and PAA are expected to show 1.5% - 3.0% growth as access to healthcare continues to improve. Standard units (used as a proxy to normalize units across regions) have decreased approximately 1.7% versus prior year, despite strong sales growth. This reflects a gradual shift to newer, premium priced agents, particularly in less developed regions.

Clarithromycin performance in AI markets continues to be strong, out-performing azithromycin sales and growth rate by almost 3 to 1. Although the ex-US quinolone class market share (15.3%) significantly lags US performance (28.4%), the quinolones show strong growth, fueled in part by new product introductions such as levofloxacin. It should be noted, however that almost 80% of Levo sales are in Japan, where sales increased 40% over the previous year. Levo launched in 1994 in Japan, but has only recently been introduced in other ex-US markets. Moxifloxacin was launched Q4 1999 in Germany, and has begun roll-out to other European markets in 2000. Moxi has not yet been submitted in Japan. Gatifloxacin approval is expected for European markets in Q2 2001, and is currently in Ph III for Japan. Cephalosporins continue to dominate the ex-US market, with sales share of over 40% (compared to only 17% in the US).

Table B 3.b Ex-US Sales

		1999 Sale	s	199	9 Standa	rd units
	Sales (\$000s)	Share	Growth (99/98)	SU (000s)	Share	Growth (99/98)
Penicillins	\$2,475	21.2%	0.8%	NA	NA	NA
Augmentin	S684	5.9%	1.9%	1,213	6.4%	2.0%
Amoxicillin	S684	5.9%	-8.1%	3,479	18.3%	-1.9%
Cephalosporins	\$4,948	42.3%	7.5%	NA	NA	NA
Cefacior (Ceclor)	S344	2.9%	-8.0%	638	3.4%	-8.9%
Cef. Axetil (Ceftin)	\$288	2.5%	2.9%	261	1.4%	2.7%
Cef. Proxetil (Vantin)	S185	1.6%	7.0%	186	1.0%	3.9%
Ext. Spec. Macrolides	\$2,257	19.3 %	5.1%	NA	NA	NA
Clarithromycin	S904	7.7%	12.0%	816	4.3%	8.3%
Azithromycin	\$344	2.9%	4.1%	113	0.6%	4.6%
Roxithromycin	S253	2.2%	0.1%	257	1.4%	-0.8%
Quinolones	\$1,788	15.3 %	11.1%	NA	NA	NA
Ciprofloxacin	\$530	4.5%	1.2%	404	2.1%	4.7%
Levofloxacin	\$467	4.0%	54.0%	248	1.3%	31.2%
TOTAL	\$11,685	100%	5.9%	19,031	100%	-1.7%

Source: IMS retail pharmacy data for all formulations, all audited ex-US markets; standard units used as a proxy for prescription market share, since Rxs are not audited in most ex-US markets

B.4 Current Treatment Options

Class	Mechanism of Action	Comments		
Penicillins Cell wall synthesis inhib		Mostly generic, class has seen significant decrease as a result of penicillin resistance		
Cephalosporins	Cell wall synthesis inhibitor	Some generic, class has seen significant decrease in use as a result of prevalence of B-lactamase producing strains		
Tetracyclines	Protein synthesis inhibitor	Generic agents, relatively high levels of resistance but are still useful in some indications		
Sulfonamides Folic acid synthesis		Generic agents, relatively high levels of resistance but are still useful in some indications		
Macrolides	Protein synthesis inhibitor	Widespread use in RTI, macrolide resistance has been increasing rapidly, but has not yet translated into declines in clinical efficacy; II, flu activity continues to be class weakness, along with GI events, drug-drug interactions, & taste perversion		
Quinolones	DNA synthesis inhibitor	Fastest growing antibiotic class, used in broad spectrum of indications; class historically associated with poor Gram+pathogen coverage and sub-optimal safety profiles; newer agents (Levaquin, Tequin, Avelox) have improved dramatically along both spectrum and safety dimensions.		
Oxazolidinones	Protein synthesis inhibitor	Newest antibiotic class to reach market, due to limited Gram profile and potential safety issues will be used primarily in nosocomial setting		

Competitive Analysis – Emerging Competition **B.5**

	Table B.5a Pipeline									
Product	Company	Class	Phase/Estimated Time to Market	Country	Comment					
Ketek (telithromycin)	Aventis	Ketolide	Filed 3/00 Est. launch 3/01	U.S.	Respiratory indications; filed NDA 3/00; 800 mg QD; first in ketolide class to reach market.					
Factive (gemifloxacin)	SKB	Quinolone	Filed 12/99 Est, faunch 12/00	US	Superior to other quinolenes for MRSA; highly potent vs. RTI pathogens II. flu, M. eat and S. pneume and UTI pathogens E. coli and P. mirabilis, CRSP; potency > spar, trov, grep and ≥ moxi; activity vs. P. acruginosa?; good atypical and mycoplasma coverage; intracullular penetration; low photo/CNS tox; 700 patient database					
Sitafloxacin	Daiichi Seiyaku	Quinolone (IV only)	III II Est. launch 2002	Japan U.S., Europe	Potent against MRSA, pseudomonas and bacteroides activity; diarrhea, Al II, low WBC, phototox issues; will likely target severe rather than community infections					
Ecenofloxacin	Chiel Foods	Quinolone	ll Est. launch 2002	UK	Active against CTI and RTI pathogens; superior to lome and offo vs. P. aeruginosa. The = 14-19 hr; will likely be target to severe rather than community infections					
C\$-940	Sankyo	Quinolone	II Est. launch 2002	Japan	Active against G+/-; excellent activity against II. flu, c. jejuni, M. pneumo, and C. trachomatis; greater potency than cipro; tu2 ~ 1 hr; BA~80%					
Т-3811	Toyama/BMS	Quinelene	I Est. launch 2005	Japan	Excellent potency and low toxicity					
ABT-492	Abbott	Quinolone	Pre-clin Est. launch 2005	US	Excellent potency, good anti-pseudomonal activity. To initiate phase 111/00					
DC-756	Daiichi Pharma	Quinolone	Pre-clin Est, launch 2006	Japan	Low toxicity; in vitro potency ≥ trova, STTX & HSR-903					

B.6 Unmet Needs

Overall unmet need in the anti-infective market is low. Resistance represents the largest unmet need, which will continue to evolve over time. Satisfaction with other product attributes, such as convenience, spectrum of activity, and tolerability/safety is quite high. Any improvements in these areas will be incremental and will offer little in the way of differentiation. Table B.6a shows the impact of the pipeline on current unmet market needs.

Table B.6a Unmet Market Needs and the Impact of the Pipeline			
Unmet Need	Pipeline Impact		
Activity against resistant organisms	Strep. pneumo, MRSA, and VRE represent most problematic pathogens although new quinolones/ketolides do well with most resistant Strep. pneumo strains; quinolone-resistant Strep. pneumo may develop; pseudomonas resistance is also increasing; resistance will likely continue to be a source of unmet need due to its dynamic nature.		
Low propensity for resistance development	Given that most compounds in development are from classes of drugs already in use, this need is largely unmet. Unclear how quickly resistance will build to new classes of drug; gatifloxacin claims 8-methoxy functional group results in lower propensity for resistance development		
Convenience (duration/frequency)	Standard moves toward 5-7 days of therapy with QD dosing; may start to see 3-day therapies for some indications (AECB)		
Increased tolerability	While some degree of unmet need exists, increasingly, agents (which have not been withdrawn) are reaching the marketplace with adverse event profiles that approach clinical insignificance; a very clean safety profile should be regarded as a necessary component rather than a differentiating one		
Few drug-drug interactions	Quinolones, macrolides, and ketolides all interact with other drugs to varying degrees; a potent drug with no interactions would be a benefit in this market		

C. Product Positioning

C.1 Product Positioning Options

Positioning Alternative	Strategy	Strengths	Weaknesses
Macrolide replacement	Convert existing macrolide business (including Biaxin) to	Relatively simple strategy to implement & communicate to	Sales are at expense of Biaxin
	ABT-773. Desirable if Biaxin XL erosion is expected to be high upon	market	Will need to achieve a very good tolerability & convenience profile
	launch of IR generics	Large Zithromax business to target	to maximize this strategy
		Strategy is a natural extension of 773's activity against macrolide-	May be difficult to keep business from shifting toward generic
		resistant S. pneumo	clari/azi
Second line (macrolide-sparing)	Co-position Biaxin and ABT-773. Desirable if Biaxin XL erosion is expected to be low upon launch of	Sales of 773 would be at least partially additive to Biaxin	Can be difficult to segment & communicate to reps/physicians
	IR generics	Support of both Biaxin and 773	
	In generics	may allow a broader scope of the	
		RTI market to be served	
		Allows for greater flexibility with	
		price, potential for advantageous price/volume scenarios	
Octobra Goldon	Doubles on a start of the other to		Mari Carlottania
Quinolone fighter	Position as a potent alternative to quinolones for RTIs	RTI-specific spectrum of 773 could play well if quinolone	May be difficult to convince physicians that 773 is as potent.
		resistance develops	
		1911 10 4 5770.1	II. flu activity of 773 is inferior to
		RTI-specific spectrum of 773 is consistent with "appropriate use"	quinolones
		Quinolones are fast-growing	
		market segment	

C.2 **Target Product Profile**

C.2.1 ABT-773 Target Product Profile

Table ${
m C.2.1}$ outlines the desired target product profile for ABT-773

	Date		Confirm	Share
Attribute	Defined	Probability*	Status	Impact
Activity against Gram +. Gram atypicals	3/1997	High	Confirmed	High
Activity against <i>H. influenzae</i> = azi	3/1997	High	Confirmed	High
Active against 80% of Gram + resistant strains of efflux and MLS-c	3/1997	High	Confirmed	High
Active against most macrolide resistant pathogens on a bacterial-worldwide- susceptibility panel	3/1997	High	Confirmed	High
ncidence of GI side effects=azi	3/1997	Low	Not Met	High
ncidence of drug-interactions = clari, no contraindications	3/1997	High	6/2001	Medium
QD dosing adult/tablet	3/1997	Medium	6/2001	High
QD dosing ped OS	3/1997	Medium	9/2000	Medium
QD dosing for IV	3/1997	Medium	12/2000	High
Comparable pain at injection site than azi		Medium	12/2000	Low
Less metallic taste than clari XL	3/1997	Medium	6/2001	High
OS equal in taste to Azi, Omnicef		Low	9/2000	High
5-day therapy for most indications	3/1997	Low	6/2000	High
COGS > 80% SMM at launch	3/1997	High	12/2001	Low
Maintain balanced plasma/tissue levels similar to clari		Medium	12/2001	Medium

^{*} Probability Key: High = 70-100% Medium = 30-69% = 0-29% Low

Table C.2.2 outlines the product profile strengths, weaknesses, opportunities and threats.

Т	Table C.2.2 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)					
CATEGORY	ITEM (Probability/Impact)	STRATEGY				
	Macrolides/ketolides are regarded as an "appropriate" choice for RTIs; could be used to advantage should quinolone resistance develop	Leverage recent guidelines to develop support for class in RTIs; monitor quinolone resistance surveillance				
Strengths	ABT-773 is generally regarded as more potent than telithromycin and macrolides against Grampositive causative RTI pathogens, including resistant pathogens	Utilize in vitro and animal model data to build conceptual argument for 773 relative to telithromycin and other agents via advisory panels, symposia, etc.				
	ABT-773 may offer unique mechanistic advantages relative to telithromycin and macrolides (ribosome binding)	Utilize in vitro and animal model data to build conceptual argument for 773 relative to telithromycin via advisory panels, symposia, etc.				
	Potential for perceived weakness of product with respect to PK profile at 150 mg dose	Identify strategy to "explain" clinical data in light of PK issue; "ribosome story"				
Weaknesses	H. flu microbiological activity inferior to quinolones	May be able to mitigate if clinical eradication data is strong; re-evaluate after receipt of phase III data				
	Phase II data suggests moderate levels of diarrhea and taste perversion	Telithromycin appears to have even higher diarrhea rate; consider phase IIIb/IV comparative study				
Opportunities	Potential for I.V. formulation, has positive impact on image of tablet	Continued funding of IV program				
Opporumues	Potential for pediatric formulation, has positive impact on image of tablet	Make go/no-go decision based on taste/PK data				
	May be BID dosing for CAP and/or sinusitis-all recent antibiotics have QD dosing for all indications	Proceed with dose ranging phase III to determine if QD dosing is adequate for these indications				
	II. flu eradication may be sub-standard at 150 mg dose	Evaluate in light of phase IIIa data (2Q01)				
Threats	Telithromycin may gain 5-day indication for sinusitis-no other antibiotics have 5-day claim	In light of phase IIIa data, evaluate whether 5-d vs 10-d ABT-773 arm could be added to gain 5-day indication				
	Requisite number of resistant isolates for claim may not be achievable for NDA; may require additional trials	Evaluate situation at completion of phase III clinical program				

C.2.2 Target Product Label - See Appendix 1

C.3 Reimbursement/Pricing Strategies

C.3.1 Reimbursement/Managed Care

Development of reimbursement strategies will be initiated upon completion of the phase IIIa studies, at which time product dosing will have been determined and more certainty to efficacy/AE rates will have been obtained.

C.3.2 Pricing Strategy

- a) U.S pricing for 5 days of ABT-773 will be at parity with 5 days of Zithromax, allowing ABT-773 to effectively compete for Zithromax business.
- b) Pricing in most European markets will be set by the government, and will be somewhat dependent on how the ketolide is classified – as a macrolide or as a new class that merits a price premium vs. the macrolide class. Although a price premium would increase revenue per unit, it could potentially limit market penetration, and therefore, reduce total revenue opportunity. Clari will be subject to downward pricing pressure due to European and Japanese price control measures and to generic incursion in LA and PAA markets over the next few years. Therefore, the base case pricing assumption is that ABT-773 will achieve pricing comparable to current clari price per course of therapy.

C.4 Sales Forecast(s) for ABT-773

C.4.1 U.S. Sales Forecast

The U.S. forecast is shown in Table C.4.1a, below:

Table C.4.1a U.S. Forecast (Date of Forecast: 7/00)					
	2004	2005	2006	2007	2008
Market (MM TRX)*	195	193	191	189	187
- % chg	-1.0%	-1.0%	-1.0%	-1.0%	-1.0%
Abbott Share (%)	2.1%	3.2%	4.2%	5.3%	6.2%
Abbott TRX (MM)	4.1	6.2	8.1	10.0	11.7
Price/Rx (\$, avg)	\$35	\$34	S32	S33	534
Abbott Sales (\$MM)	\$139	S199	\$265	S335	\$399
R&D (\$MM)	\$30	\$30	530	530	520
SG&A (\$MM)	\$101	\$83	586	599	\$115
SMM (%)	88%	90%	90%	90%	91%
Div. Margin (SMM)	(\$23)	\$44	S95	S138	\$174

10 year pre-tax NPV @ 12.5% = \$345MM

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$201MM

10 year post-tax ENVY @ 12.5% = TBD

Key Assumptions:

- U.S. approval August 2003
- Market is declining 1% per year on TRX basis
- 150 mg QD dosing for all indications
- 5 day AECB & pharyngitis; 10 day CAP & sinusitis
- 5 day pack priced at parity to Zithromax; average price per RX shown is after discounts/rebates
- 800M details/year (62% primary, 38% secondary)
- Sampling at parity to current Biaxin levels on basis of courses of therapy sampled
- Peak market share = 6.9% (2009)
- U.S. R&D costs at 60% of total
- NPV does not account for potential cannibalization of Biaxin by ABT-773

Forecast Update Plan:

Forecast will be updated if necessary upon receipt of the phase IIIa data 2Q01.

C.4.2 Ex-U.S. Sales Forecast The ex-U.S. sales forecast is shown in Table C.4.2a, below.

Table C.4.2a Ex-U.S. Forecast (Date of Forecast: 8/00)					
	2004	2005	2006	2007	2008
Market (MM packs)*	592	592	593	594	595
- % chg	0.0%	0.0%	0.1%	0.2%	0.2%
Abbott Share (%)	1.1%	2.3%	3.3%	4.3%	4.9%
Abbott packs (MM)	6.5	13.6	19.7	25.3	29.3
Price/Rx (\$)	12.6	12.6	12.6	12.6	12.6
Abbott Sales (\$MM)	82	172	248	321	373
R&D (\$MM)	4	2	2	2	2
SG&A (\$MM)	84	84	84	76	76
SMM (%)	85%	88%	89%	90%	90%
Div. Margin (SMM)	(19)	63	132	199	254

¹⁰ year pre-tax NPV @ 12.5% = \$403MM

Key assumptions:

- Ex-US launch lags U.S. by 6-18 months due to pricing negotiations and/or special registration requirements in AI markets
 - Europe (average): U.S. launch + 6 months = Q12004
 - LA (average): U.S. launch + 6 months (Q1 2004)
 - PAA (average): U.S. launch + 1 yr (Q3 2004)
 - Japan (average) = US launch + 1 yr (Q3 2004)
 - Canada = US launch + 12-18 mos (Q3 2004)
- Market is declining approximately 1-2.5% in Europe, Japan and Canada, but increasing approximately 2-3% in LA and PAA
- ABT-773 Pack Price = current Clari price per course of therapy
 - Europe: \$10.8./pack (150mg, 5 day); \$22.6/pack (300mg, 7day avg)
 - LA/Canada: \$13.4/pack (150mg, 5day); \$28.2/pack(300mg, 7 day avg)
 - PAA: \$9.7/pack; \$20.4/pack
 - Japan; \$12.8/pack; \$26.8/pack
- Peak Market share (2008): Europe = 6.0%; LA/Canada = 4.6%; PAA = 3.3%; Japan = 5.9%; 90% of pack share from 150mg QD dose strength
- Dosing = 150mg QD 5 day for bronchitis and pharyngitis; 300mg QD 10 day for CAP and sinusitis
- No resistance claim, however, language in label describing in vitro activity against resistant organisms

Forecast Update Plan:

Forecast will be updated by 12/00 after 2001 LRP forecasting cycle, incorporating input from AI affiliates.

¹⁰ year pre-tax ENVY @ 12.5% = TBD

¹⁰ year post-tax NPV @ 12.5% = \$234MM

¹⁰ year post-tax ENVY @ 12.5% = TBD

^{*} packs used as a proxy for Rxs (Rxs not audited in most AI markets)

C.5 Facilitating Launch and Market Penetration

There are three components of the strategy to facilitate the launch of ABT-773. These are 1) promotional claims 2) communication strategy 3) opinion leader development. These activities are summarized in thesections below.

C.5.1 Desired Promotional Claims

Desired key message	Regulatory requirement	Measure	Timing	Study Number	Type of message	Probability	Share Impact	Comments/Risk
Low potential for resistance development	тво	Mutation frequency, sub- MIC social passages, mutation prevention concentration	In progress	Multiple	In-vitro (implied efficacy)	Medium	Med	
Does not induce macrolide resistance	TBD	Ribosome kinetics, MIC evaluations	In progress	Multiple	In-vitro (implied efficacy)	Medium	Med	
Claim against penicillin/mac resistant S. pneumo	~ 15 resistant isolates, high crad. rate	Patient isolates, crad rate (CAP)	5/2002	Phase III studies	Efficacy	Low	Med	
Lower resource utilization vs comparators	2 cluiical studies	Overall disease cost.	5/2002	Phase III studies	Economic	Low	Med	
Comparable curc/cradication rates to phase III comparators	Clinical studies	cure/erad rate	5/2002	Phase III studies	Efficacy	Medium	High	
Comparable safety/AE profile to phase III comparators	Clinical studies	safety/AB rate and severity; dropout rate	5/2002	Phase III studies	Efficacy	Medium	High	

C.5.2 Communication Strategy

Following is a summary of the activities to date relating to communication strategy:

- -83 posters have been presented at 8 scientific conferences between 1998-2000
- -8 journal articles have been published in two journals, all published in 2000
- -Approximately 72 research studies have been completed, many with the intent to publish
- -Approximately 87 research studies are in progress, many with the intent to publish
- -Approximately 120 external investigators have completed or are in progress with research studies, many with the intent to publish

Much of the above work has dealt with microbiological and/or animal model data. As the compound moves forward, emphasis will shift to the release of more clinically relevant data. Scientific meetings and journals will continue to serve as the primary channels for dissemination of information, though more specialized communication (symposia, advisories, press releases, etc) will start to be used as a more complete understanding of ABT-773 is gained.

An additional focus of study/communication will be towards capitalizing on the unique ribosome binding properties of the product. Information gained from this initiative may be called upon in defense of the selection of the relatively low 150 mg dose. It may also serve as a means of differentiating the product. Various internal and external investigators are working to gain a greater understanding of the underlying science as well as the properties of ABT-773 in this area. Early in 2001 an internal/external "working group" will be convened to develop a strategy for further study in this area and for the optimal dissemination of this data.

Management of all aspects of the ABT-773 communication plan will be facilitated via an intranet tool currently in development by IM&T and external developers. The completion is targeted for November 2000.

C.5.3 Opinion Leader Development

An ABT-773 advisory board of external opinion leaders has been established and has been convened several times over the last several years. The purpose of these advisories has been to solicit guidance for the development of ABT-773 as well as to positively influence their perception of the ketolide class and ABT-773 in particular. An additional mechanism for opinion leader development has been their involvement in both clinical and non-clinical studies. Approximately 120 external investigators, many regarded as top-tier opinion leaders, have experience with ABT-773. A major initiative as ABT-773 moves forward is to identify key national opinion leaders who have favorable experience/opinion of ABT-773 and to work with them to develop an advocacy strategy for publications, scientific meetings, symposia, and advisories.

D. Regulatory Strategy

D.1 Regulatory Strategy SWOT Analysis

T	able D.1 SWOT Analysis (Strengths/Weaknesses/	Opportunities/Threats)			
CATEGORY	ITEM (Probability/Impact) STRATEGY				
Strengths	QD dosing may be viewed as positive for patient compliance if data is strong	Make sure PK/PD data is available to support dose selection rationale			
	If the drug has a favorable risk benefit ratio with added value compared to existing therapies then the likelihood of approvability is high in EU countries or other countries requiring a CPMP package	The development programs must be designed to unequivocally demonstrate the existence of an added value (e.g. safety or clinical efficacy against resistance species)			
	ABT-773 may present a key point of differentiation with promising activity against macrolide and penicillin resistant Streptococcus pneumoniae and enhanced antibacterial activity in vitro. If proven in vivo, this may indicate favourable relative therapeutic value required for approval and inclusion within local use guidelines.	To utilize the enhanced bacterial activity as a key point of differentiation need to: •Ensure clinical program is designed to optimize chances of obtaining desired isolates •Ensure appropriate pk/pd studies are performed •Seek agreement from FDA regarding burden of proof for labeled indication against resistant pathogens			
	For COFs countries, if the US or EU receives approval then approvals in these LA/PAA countries are assured assuming appropriate sourcing.				
Weaknesses	Take with food labeling is required to reduce ATVs	FDA will still require pivotal bioavailability studies to be done in fasted state.			
	If BID is chosen for either CAP or ABS, diurnal variation may become an issue during FDA review	Justification must be provided			
	Conformance to Abbotts' & FDA's Electronic Document Management System requirements may impact filing date	Electronic filing likely to be valued very highly by FDA, so need to manage internal process to see that we can meet requirements			
	High COG's for bulk drug driving vendor matrix and push to redefine starting material	Need FDA buy-in from End-of-Phase 2 CMC meeting on starting material and vendor matrix, including stability requirements			
	Harmonization of global clinical trial designs and	Communicate with team, international affiliates, international experts and			

		23
	guidelines Differences in medical practice exist worldwide for antibiotics and associated infections Differences in comparator and dosing regimens Stringent EU regulatory environment with antibiotics	discuss with EU authorities through agency meetings to ensure design of trials and comparators are acceptable
	EU filing will require a harmonized labeling therefore country-speicfic favourable labeling cannot be pursued (as done with clarithromycin)	Discuss any country specific issues with authorities, international experts and affiliates. Monitor regulatory environment and competitive products.
	Two dose scenario with a lower dose chosen for ABECB, Sinusitis and Pharyngitis with a second dose chosen for CAP may provide limited numbers to assess safety of the higher dose	Discuss issue authorities at agency meeting and ensure MAA addresses this issue. May consider Phase IV studies to address this concern.
	Increased resistance awareness may influence stricter requirements and trend away from lowest effective dose	Ensure clinical program includes relative pk/pd studies and can demonstrate clear efficacy at proposed doses. Ensure clinical program is designed to obtain resistance isolates
Opportunities	Labeling for resistant organisms if isolates are obtained	Get agreement with FDA at End of Phase 2 meeting regarding number of isolates required for labeling claim
	Eligible for Centralised filing process which would provide EU-wide 10 year protection. May also file by Mutual Recognition procedure which more provides flexibility for non-harmonized disease practices (e.g. infectious disease/antibiotics)	Filing strategy to be determined based on strength of the clinical program and advice received from agencies during planned agency meetings
	Once Daily Dosing may enhance compliance	
Threats	QT prolongation class labeling in Warnings section of labeling	Get agreement with FDA at End of Phase 2 meeting regarding EKG monitoring in Phase 3 and promote theory that QT prolongation is not class related Ensure that non-clinical and clinical program fulfill the CPMP points to consider on QTe prolongation.
	Liver enzyme increases in Warnings section of labeling	Ensure that non-clinical and clinical program addresses potential safety

	labeling issues and MAA/NDA addresses these concerns.
Possible failure of short course therapy for Pharyngitis due to more stringent Test of Cure requirement from FDA	
If gastrointestinal AE's are high, may affect benefit/risk assessment by FDA	
Could be affected by CDC push to reduce antibiotic use; reserve use of drugs effective vs resistant organisms until existing therapies have failed.	

Registration Strategy and Timelines for Filing

Table D.2 R	Table D.2 Registration Strategy and Timelines for Submission					
REGION	Proposed Submission Date	Justification				
US	August 2002	Estimated completion of the clinical program and CMC stability data				
Europe Filing procedure (Centralised or MRP) to be determined based on strength of clinical data and discussion with authorities	August 2002	Estimated completion of the chemistry/pharmacy and clinical data				
Japan Plan to bridge to US data assuming pk profile is similar in Japanese subjects and a successful Phase II bridging study is possible in Japan	TBD, after completion of Phase I local study in Japan.	Bridging obviates the need for a lengthy and expensive Japanese Phase III program. Requires Kiko agreement.				

EXHIBIT 608 Part 2

D.3 Data Requirements and Impact on CMC/Non-Clinical/Clinical Program

Table	Table D.3 Data Requirements and Impact on CMC/Non-Clinical/Clinical Program					
COUNTRY	Guideline Requirement	Probability of Achieving	Impact on Filing	Impact on Approvability		
US	Draft Anti-Infective Guidances for CAP, ABECB, ABS & Pharyngitis	High	Iligh	Iligh		
	Draft Anti-Infective Guidances General Considerations for Clinical Trials	High	High	High		
	Anti-Infective Points to Consider document	High	High	High		
	ICH Efficacy Guidances – E1 through E12	High	High	High		
	ICH Safety Guidances – S1 through S7	High	High	High		
	ICH Quality Guidances – Q1 through Q7	High	High	High		
Europe	All ICH guidelines as above, plus CPMP points to consider on QT prolongation CPMP guideline on the clinical evaluation of antibacterials DRAFT CPMP guideline for pk/pd	High/Moxlerate	High	High		
Japan	All ICII guidelines as above plus local guidelines/JP issues. ICII E5 ethnic bridging guideline.	Moderate/Unknown	High	Iligh		

D.4 Table of Proposed Discussions with Health Authorities

	Table D.4 Table of Proposed Discussions with Health Authorities						
COUNTRY	Reason for Discussion	Proposed timing for Discussion					
US	End of Phase 2 – Clinical	10/20/00					
	End of Phase 2 CMC	TBD					
	Pre-NDA Clinical	TBD					
	Pre-NDA – CMC	TBD					
Europe	Individual agency meetings with UK, Germany, France and Spain to discuss Phase III Clinical program trial designs Profiles proving to be described based on	UK complete – 07/10/00 Germany complete - 07/21/00 France scheduled – 08/30/00 Spain – to be determined					
	Pre-filing meetings to be determined based on filing strategy						
Japan	KIKO- discuss bridging strategy to 300 mg EU/US program	Complete June 2000					
	KIKO re-discuss dose justification	TBD					

E. Development Cost and Sensitivity Analysis

E.1 Strategic Spending Overview

The tables below describe the major milestones for the ABT-773 Tablet program as well as the Phase II/III studies and associated costs.

Metrics Dates	
Description	Date
DDC Meeting	3/1997
Start of first GLP animal tox study	6/1997
First dose in human (beg. Phase I)	12/1997
First dose in patient (beg. Phase II)	9/1999
First dose in Phase III	11/2000
Last Patient/Last Visit	4/2002
NDA Filing	8/2002
NDA Approval	8/2003
Europe (EMEA) Filing	8/2002
Europe (EMEA) Approval	8/2003
Japan l'iling	TBD
Japan Approval	TBD

Protocol # - Study Name	Start (1st <i>Pt</i>)	End (Last CRF)	R/OSS \$000	Total Target Patients	Actual Enrollment
·	•	<u> </u>			
M99-048, Phase II Dose Ranging, ABECB	9/1/99	3/31/00	3,885	300	384
M99-053, Phase II Dose Ranging, Sinusitis	9/1/99	4/30/00	3,172	300	292
M99-054, Phase II Dose Ranging CAP	9/1/99	4/30/00	4,089	300	187
M00-219 Phase III CAP, Dose Ranging	11/7/00	4/30/01	14,400	800	0
M00-216 Phase III ABECB vs Azithromycin US	11/7/00	4/30/01	7,381	600	0
M00-217 Phase III ABECB vs Levofloxacin EUR	11/7/00	4/30/01	4,600	500	0
M00-225 Phase III Sinusitis Dose Ranging	11/7/00	4/30/01	7,200	600	0
M00-223 Phase III Pharyngitis vs Penicillin US	11/7/00	4/30/01	4,340	520	0
M00-222 Phase III Pharyngitis vs Penicillin EUR	11/7/00	4/30/01	5,000	520	0
M00-226 Phase III Sinusitis vs Augmentin US	10/`1/01	4/30/02	4,400	450	0
M00-220 Phase III CAP vs Amoxicillin EUR	10/ 1/01	4/30/02	5,700	500	0
M00-221 Phase III CAP vs Levofloxacin US	10/`1/01	4/30/02	8,200	450	0
M00-218 Phase III Sinusitis vs quinolone TBD EUR	10/ 1/01	4/30/02	5,300	500	0

E.2 Base Case Scenario

E.2.a Base Case Scenario for Project:

	Prior Years	1999	2000	2001	2002	
Base Program						
CMC	17.5	28.6	31.2	22.8	14.5	
- PARD/IDC	4.8	5.4	8.6	7.8	4.5	
- SPD	12.7	23.2	22.6	15.0	10.0	
Drug Safety	3.5	2.5	3.4	1.7	1.0	
Other:	7.4	7.7	5.0	4.6	4.0	
To	tal 28.4	38.8	39.6	29.1	19.5	
Clinical Program						
Registration	2.5	9.5	34.5	61.9	23.3	
Pricing						
Marketing						
Other:						
To	tal 30.9	48.3	74.1	91.0	42.8	287.1

E.3 Upside Scenario

Funding Increase

If funding were to be increased by 25%, how would that increased funding be used?

- 1) Accelerating Program
 - · At this point in the program, additional funding will not accelerate the filing any earlier than the August 2002 date. The current program is intense and needs to be accomplished within a short timeframe. Probability of success in the current program is estimated at 50 to 60%.
- 2) Enhancing Program
 - The pediatric and IV formulations are currently not funded and could continue from the earlier work completed in 2000. Approximately \$21MM is required for the IV development and S39MM for the pediatric development. The IV program would provide support for marketing this antibiotic for serious infections and help the marketing of the tablet, and the pediatric supports the marketing position that this is a safe drug.
- 3) Enhancing Program within Existing Program
 - · Additional funding within the current program would allow for additional patient enrollment incentives or an increase in the number of sites participating in the current Phase III program. This would increase the probability of success in achieving the Aug 2002 filing date.

E.4 Downside Scenario

Funding Decrease

If funding were to be decreased by, how would that decrease be applied?

- 1) Slowing Program
 - A decrease in program spending would delay the filing of ABT-773 significantly, minimum one year, as RTI indications are seasonal, and the majority of patient enrollment comes from the northern hemisphere.
- 2) Trimming Program
 - Eliminating an indication will cause this filing to be unapprovable as the number of required patients on drug and the four indications being are sought are the minimum RTI indications for approval. The program is only funded currently for one formulation.
 - The current program is currently funded at the minimal acceptable level for approvability by both FDA and AI regulatory agencies.
- 3) Increasing Risk
 - Refer to Item 2 above. Current probability of success for the program is 50 to 60%. Any reduction to the program will significantly delay the filing.

F. Pharmacokinetics/Pharmacodynamics/Phase 1

F.1 PK/PD/Phase 1 SWOT Analysis

Strengths, weakness, opportunities and threats regarding the clinical program for ABT-773 are discussed below:

Table F.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)						
CATEGORY	ITEM (Probability/Impact)	STRATEGY				
Strengths	Phase IIb clinicals and PK/PD data support once daily dosing.	Conduct Phase III for ABECB and pharyngitis at 150mgQD. Further examine 150mgQD for AMS & CAP.				
	Food has no influence on ABT-773 PK. High drug levels in alveolar macrophages.	Tolerability may require administration with food. This may explain efficacy vs. If flu.				
Weaknesses	ABT-773 may require a total daily dose of 300mg for severe infections.	Examine 150mg BID for AMS & CAP and conduct tissue level studies.				
	ABT-773 is metabolized by and inhibits CYP3A; has potential to cause clinically important drug interactions.	Lowest effective dose (150mgQD) may minimize drug interaction potential.				
	ABT-773 has low & variable oral bioavailability. Absorption "window" makes ER dosage forms not feasible.	Multiple ER dosage forms tried, none provided adequate bioavailability and true extended release in vivo.				
Opportunities	At 300mgQD, ABT-773 inhibits CYP3A, but inhibition is less than 250mgBID clarithromycin.	May wish to repeat midazolam (CYP3A substrate) interaction study at 150mgQD or BID.				
Threats	Disappointing ABT-773 tissue levels (especially WBC and ELF). Competition (Ketek TM) reports higher WBC and ELF levels.	Repeat tissue level studies and in the meantime focus on efficacy data.				

F.2 PK/PD (Clinical)

The Phase 1 program consists of pharmacokinetic, special population, interaction and tissue penetration studies as outlined in section F.3. To attempt to design a once daily dosage form with optimal pharmacokinetics, fifteen prototype formulations were developed for the initial investigations of preliminary safety and pharmacokinetics. Three immediate release and twelve extended release formulations were evaluated with immediate release capsule formulation (IR-A) serving as the reference formulation. After a review of the preliminary data of these studies, an immediate release tablet formulation (IR-C) was chosen for further development based on

pharmacokinetics, safety, and ease of manufacture. Studies in special populations, drug-drug interaction assessments and tissue penetration evaluations have been conducted with formulation IR-C.

Table F.2.a lists all the completed, planned and proposed PK/PD clinical trials for ABT-773:

	Table F.2.a: Clinical PK/PD Trials (Phase 1)							
STUDY	POPUL ATION	OBJECTIVE/ PURPOSE OF STUDY	# OF PATIENTS	FUNDED?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS			
M99-105	Healthy Adults	PK of ABT-773 in WBC Relative to Plasma	N = 8	Study completed	Poor partitioning of ABT-773 into WBC.			
M99-007	Healthy Adults	Compare Concentrations of ABT-773 in BAL & AM to Plasma	N = 43	Study completed	High concentrations of ABT-773 in AM. Relatively low concentrations in ELF.			
M99-142	Healthy Adults	Compare Concentrations of ABT-773 in BAL, ELF, AM, CSF & TLT to Plasma	BAL = 50 CSF = 10 TLT = 10	Ongoing				

F.3 Phase 1 Overall Summary

Pharmacokinetic and Safety Studies:

In the first Phase 1 study (M97-716), the pharmacokinetics and safety of ABT-773 (IR-A) were assessed following rising single oral doses (100 – 1200 mg). This study was conducted in two parts with Part I consisting of single rising doses under fasting conditions and Part II a food effect assessment at a single dose of 400 mg. The pharmacokinetics of ABT-773 were linear over the 400 mg to 1200 mg dose range. At doses below 400 mg, the pharmacokinetics appeared to be nonlinear, with AUC increasing more than proportionally with dose. More recent data have indicated that safe and effective doses of ABT-773 in patients will likely be below 400 mg/day and that pharmacokinetic nonlinearity will occur at these clinically-relevant doses. The mean half-lives over the 200 – 1200 mg dose range were between 5.3 - 6.7 hours. Administration of ABT-773 under nonfasting conditions had little or no effect on the pharmacokinetics. The most commonly reported adverse events were taste perversion and/or events related to the gastrointestinal system including abdominal pain, nausea, vomiting and diarrhea. Administration of ABT-773 with food decreased or eliminated the gastrointestinal adverse events but did not affect the incidence of taste perversion.

In the second Phase 1 study (M97-796) the pharmacokinetics and safety of ABT-773 (IR-A) were assessed in a multiple rising dose study. Total daily doses ranging from 200 mg to 1000 mg were administered for seven days. Over the multiple dose range of 200 to 500 mg BID and 200 to 300 mg TID, the pharmacokinetics of ABT-773 appeared to deviate from dose proportionality and time-linearity. The AUCs increased more than proportionally with increasing dose, and accumulation from single- to multiple-dose administration was greater than predicted. At steady state, the half-life ranged between 6.0 and 8.8 hours. ABT-773 pharmacokinetics exhibited diurnal variation, with lower Cmax and AUC values for doses administered in the afternoon or evening than for doses administered in the morning. In groups who were administered total daily doses of ≥600 mg of ABT-773, the most frequently reported adverse event was taste perversion.

In the third Phase 1 trial (M98-889) the relative tolerability of two doses of ABT-773, 100 mg TID and 200 mg TID, was compared with that of clarithromycin 500 mg BID in 153 healthy volunteers. There were no significant differences between the incidence of adverse events between the three regimens except for taste perversion which occurred in 8% of subjects receiving ABT-773 100 mg TID, 34.6% of subjects receiving ABT-773 200 mg TID and in 37.2% of subjects receiving clarithromycin.

Three Phase 1 trials were performed to compare steady state pharmacokinetics and safety after five days of treatment with various doses of ABT-773 (IR-A); 100 mg TID vs. 200 mg TID (M99-011), 300 mg once daily vs. 200 mg once daily vs. 100 mg TID (M99-016) and 100 mg BID vs. 200 mg BID (M99-018). Over these dose ranges, the pharmacokinetics of ABT-773 deviated from linearity. As seen previously, the AUCs increased more than proportionally with dose.

Bioavailability Studies:

Two Phase 1 studies (M98-865 and M98-885) were performed to evaluate the pharmacokinetics of 600 mg once daily doses for four extended-release prototypes of ABT-773 (two per study) administered with food for four days in comparison to formulation IR-A. For the four prototypes, plasma concentration profiles were much lower than those produced by the immediate release reference capsule. As a result, none of these prototypes continued in development.

Seven further Phase 1 trials (studies M99-023, M99-024, M99-025, M99-026, M99-029, M99-035, M99-042) were conducted to evaluate the pharmacokinetics and safety of ten additional ABT-773 prototypes, two immediate release and eight extended release formulations in comparison to the reference formulation (IR-A). All studies had two, three or four period crossover designs with nonfasting, multiple once daily or BID ABT-773 5-day dosing in healthy volunteers. Pharmacokinetically, none of the extended release prototype formulations had superior bioavailability compared to the immediate release capsule. In addition, an Intelisite® study (M98-992, not included in the data package) investigating the absorption of ABT-773 confirmed that absorption of ABT-773 from the colon is limited. Due to the solubility profile of the drug, the apparent narrow absorption window, and low absorption from the colon, it appears that an extended release formulation is not feasible. Therefore, optimal bioavailability is expected with an immediate-release formulation rather than extended release formulations. Upon review of the preliminary data, the immediate release formulation (IR-C; M99-024) was chosen for further development as it appeared to be the most robust formulation and demonstrated fewer adverse events and drop-outs than IR-B (M99-023).

Additional biopharmaceutics studies will be conducted to characterize the relative bioavailability/bioequivalence and food effect on the final, production-scale tablet formulation proposed for marketing.

Table F.3.a lists all the completed, planned and proposed clinical trials for ABT-773:

	Table F.3.a: Clinical Trials (Phase 1)						
STUDY	POPUL ATION	OBJECTIVE/ PURPOSE OF STUDY	# OF PATIENTS	FUNDED?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS		
M97-716	Healthy Adults	Rising Single Oral Doses of ABT-773 in Nonfasting and Fasting Subjects	Part 1 = 56 Part 2 = 24	Study complete	ABT-773 PK were nonlinear. Food has no effect on ABT-773 PK		
M97-796	Healthy Adults	Rising Multiple Oral Doses of ABT-773	N = 83	Study complete	ABT-773 PK were nonlinear and had diurnal variation. If the final to-be-marketed regimen is QD, FDA may ask an AM vs. PM PK study.		
M99-992	Healthy Adults	ABT-773 PK Comparing Oral IR Capsule to Intelisite® Capsule (Targeted Release in Colon)	N = 10	Study completed	ABT-773 is very poorly absorbed from colon.		
M99-011	Healthy Males	ABT-773 PK Comparing 100mgBID to 200mgBID	N = 12	Study completed	ABT-773 AUC increased more than proportionally with dose and had diurnal variation.		
M99-016	Healthy Males	ABT-773 PK Comparing 300mgQD & 200mgQD to 100mgTID	N = 24	Study completed	ABT-773 AUC increased more than proportionally with dose and greater exposure achieved by QD vs. TID dosing.		
M99-018	Healthy Males	ABT-773 PK Comparing 100mgBID to 200mgBID	N = 24	Study completed	ABT-773 AUC increased more than proportionally with dose and had diurnal variation.		
M99-024	Healthy Males	ABT-773 PK Comparing 150mg IR-C Tablet to 100mg Capsule	N = 18	Study completed	Prototype C tablet was bioequivalent to the reference capsule. Greater exposure achieved by QD vs. BID dosing.		

	Table F.3.a: Clinical Trials (Phase 1) Cont.							
STUDY	POPUL ATION	OBJECTIVE/ PURPOSE OF STUDY	# OF PATIENTS	FUNDED?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS			
		Specia	al Population St	udies				
TBD	TBD	Effects of Age and Gender on ABT-773 PK		Protocol TBD	ABT-773 clearance may increase with age. Clarithromycin AUC higher in females than in males.			
M99-127	Severe Renal Impaired vs. Healthy	Effects of Renal Impairment on ABT-773 PK		Protocol in progress	No effect of renal impairment on ABT-773 PK expected.			
М99-119	Healthy Adults	ABT-773 Single and Multiple Dose Ranging PK in Japanese vs. Non-Japanese	N = 84	Study completed	At equal doses, Japanese had about 50% greater plasma ABT-773 concentrations than non-Japanese. Lower dose needed in Japanese patients.			
M99-126	Mild & Moderate Hepatic Impaired vs. Healthy	Effects of Hepatic Impairment on ABT-773 PK	N = 24	Ongoing				

	Table F.3.a: Clinical Trials (Phase 1) Cont.					
STUDY	POPUL ATION	OBJECTIVE/ PURPOSE OF STUDY	# OF PATIENTS	FUNDED?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS	
		Drug	Interaction Stu	dies		
M99-128	Healthy Adult Females	Effects of ABT-773 on the PK of OCs	N = 18	Study completed	No clinically significant drug interaction was observed.	
M99-138	Healthy Adults	Effects of Ketoconazole (CYP3A inhibitor) on PK of ABT-773	N = 18	Study completed	Ketoconazole inhibited ABT-773 metabolism increasing ABT-773 AUC >5 times.	
M99-139	Healthy Adults	Effects of ABT-773 on the PK of Theophylline	N = 18	Study completed	No clinically significant drug interaction was observed.	
M00-155	Healthy Adults	Effects of ABT-773 on the PK of Midazolam (CYP3A substrate)	N = 24	Study completed	ABT-773 inhibited midazolam metabolism doubling midazolam AUC. Interaction smaller than interaction between clarithromycin and midazolam.	
M00-156	Healthy Adults	Effects of Rifampin (CYP3A inducer) on PK of ABT-773	N = 18	Study completed	Rifampin induced ABT-773 metabolism decreasing ABT-773 AUC by >90%. ABT-773 should not be given with any drug that might induce CYP3A.	
TBD	Healthy Adults	Assessment of the Pharmacokinetic Interaction Between ABT-773 and Warfarin	TBD	Protocol TBD	R-warfarin is a CYP3A substrate and warfarin is a NTI drug.	
TBD	Healthy Adults	Assessment of the Pharmacokinetic Interaction Between ABT-773 and Digoxin	TBD	Protocol TBD	Digoxin is a Pgp substrate and a NTI drug.	

Drug Interaction Program

As indicated in the Phase 1 clinical overview, further studies in special populations and drug-drug interaction assessments will be conducted. Preliminary pharmacokinetic data are available from five drug interaction studies. Because ABT-773 will be administered to women who rely upon oral contraceptives for birth control, a study was conducted to determine whether ABT-773 affects the pharmacokinetics of the components of a commonly-used combination oral contraceptive product (Ortho-Novum 1/35). Because ABT-773 will be co-administered with

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theophylline in bronchitis patients, a study was conducted to determine whether ABT-773 affects the pharmacokinetics of the ophylline. Because ABT-773 is known to be a substrate and inhibitor of the cytochrome P450 3A4 isoform subfamily (CYP3A4) in vitro, three clinical drug-drug interaction studies suggested in PDA Guidance on in vivo drug metabolism/drug interaction were conducted. Because ABT-773 is a CYP3A4 substrate, we have examined the effects of the CYP3A4 inhibitor, ketoconazole, and the inducer, rifampin, on the pharmacokinetics of ABT-773. Because ABT-773 may be an inhibitor of CYP3A4 in vivo, we have examined the effects of ABT-773 on midazolam pharmacokinetics. Preliminary pharmacokinetic and safety data are also available from a special population study in Japanese subjects.

In addition to these five completed drug-drug interaction studies, the effects of ABT-773 on the pharmacokinetics of warfarin and digoxin will be examined. A special population study to examine the effects of mild and moderate hepatic impairment (Child-Pugh) on ABT-773 is ongoing. Because no more than 10% of ABT-773 is excreted in the urine, a reduced-design study to examine the effects of severe renal impairment (creatinine clearance: 10-29 mL/min) on ABT-773 will be conducted. An additional special population study will be conducted to examine the effects of age and gender on ABT-773 pharmacokinetics.

G. Clinical Trial Program

G.1 Clinical Trial Program SWOT Analysis

Strengths, weakness, opportunities and threats regarding the clinical program for ABT-XXX are discussed below:

Table G.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)					
CATEGORY	ITEM (Probability/Impact)	STRATEGY			
Strengths	 150 mg QD dose should minimize side effects and provide sufficient exposure for efficacy. Complete Pharyngitis, and ABECB comparative Phase III studies by 2Q, 2001, and concentrate thereafter on CAP and ABS. 	Two studies using this dose, two studies comparing it to higher dose for further evaluation in CAP and simusitis. Prepare all documentation for NDA/regulatory filings before CAP and simusitis studies complete.			
Weaknesses	 AE profile – GI, taste, at 300mg significantly higher than clari 500mg BID. Completion of CAP and sinusitis studies comparing 150 QD and BID may not occur by 2Q, 2001, delaying start of other pivotal studies. Further changes/amendments to protocols. Fail to enroll CAP and sinusitis patients early in season for Phase III trials starting 3Q, 2001. 	 Use lower dose (150 mg QD). Increase numbers of sites, work with experienced CROs, use sites in Eastern Europe. Monitor data carefully and stop study if significant trend towards one arm. Amendments will not be finalized until studies are initiated with original protocols. Increase numbers of sites, work with experienced CROs, use sites in Eastern Europe. Add South American sites if needed (2002). 			
Opportunities	Claim for resistant organisms.	Conduct studies in geographical locations where resistant bacteria are prevalent. Use central labs wherever possible.			
Threats	Studies being done by other sponsors.	Pay appropriately; maximize contact with investigators. Hold successful investigator meetings and use retainer fees if necessary.			

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G.2**Clinical Trials**

Table G.2.a fists all the planned and proposed clinical trials for ABT-773:

Table G.2.a: Clinical Trials (Phase 2-3)					
STUDY	PHASE	OBJECTIVE/ PURPOSE OF STUDY	# OF PTS	FUNDED ?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS
M00-219	III	CAP; 773 150 QD vs. 150 BID	800	Yes	11/2000 - 4/2001, 50% likely to finish on time.
M00-216	111	ABECB; comparing AZI vs. 773	600	Yes	11/2000 4/2001, 100% likely to finish on time.
M00-217	111	ABECB; comparing Levo vs. 773	500	Yes	11/2000 4/2001, 100% likely to finish on time.
M00-225	III	Sinusitis; 773 150 QD vs. 150 BID	600	Yes	11/2000 - 4/2001, 50% likely to finish on time.
M00-223	III	Pharyngitis; comparing penicillin (250 mg TID) vs. ABT773	520	Yes	11/2000 4/2001, 100% likely to finish on time. There is some chance that it will not meet FDA standards of >85% at 30 days.
M00-222	III	Pharyngitis; comparing penicillin (500 mg TID) vs. AB'1773	520	Yes	11/2000 – 4/2001, 100% likely to finish on time.
M00-221	III	CAP; comparing Levo vs. 773	450	Yes	09/2001 04/2002, 50% likely to finish on time.
M00-220	III	CAP; comparing Amoxicillin vs. 773	500	Yes	09/2001 04/2002, 50% likely to finish on time.
M00-226	111	Sinusitis; comparing quinolone TBD vs. 773	450	Yes	09/2001 = 04/2002, 75% likely to finish on time
M00-218	III	Sinusitis; comparing Augmentin vs. 773	500	Yes	09/2001 – 04/2002, 75% likely to finish on time

Phase 2

In Phase 2a study M98-967, subjects with ABECB were treated with 100 mg TID or 200 mg TID dosing regimens which resulted in high clinical and bacteriological cure rates (see Section 9.3).

Three Phase 2b studies (see Section 9.4) conducted in both the US and EU investigating ABT-773 once daily doses have been completed:

- M99-054 Community-acquired pneumonia (300 mg or 600 mg once daily for 7 days)
- M99-053 Acute bacterial sinusitis (150 mg, 300 mg, or 600 mg once daily for 10 days)
- M99-048 Acute bacterial exacerbation of chronic bronchitis (150 mg, 300 mg, or 600 mg once daily for 5 days)

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Phase 3

The Phase 3 program consists of trials originating in either the United States or Europe comparing the safety and efficacy of ABT-773 in the proposed indications as described below.

- Community Acquired Pneumonia (total n ~ 1200 for ABT-773 arms)
 - M00-221 One pivotal United States Phase 3, Controlled Study
 - M00-219 One pivotal United States Phase 3, 2 Dose Study
 - M00-220 One supportive European Phase 3, Controlled Study
- Acute Bacterial Exacerbation of Chronic Bronchitis (total n ~ 500 for ABT-773 arms)
 - M00-216 One pivotal United States Phase 3, Controlled Study
 - M00-217 One supportive European Phase 3, Controlled Study
- Acute bacterial sinusitis (total n ~ 1000 for ABT-773 arms)
 - M00-226 One pivotal United States Phase 3, Controlled Study
 - M00-225 One pivotal United States Phase 3, 2 Dose Study
 - M00-218 One supportive European Phase 3, Controlled Study
- Pharyngitis (total n ~ 500 for ABT-773 arms)
 - M00-223 One pivotal United States Phase 3, Controlled Study
 - M00-222 One supportive European Phase 3, Controlled Study

Strategy of Clinical Program

A global clinical development program has been implemented intended for world-wide registration. An estimated total of 5,500 subjects will be enrolled in the Phase 3 clinical program including both study drug and comparator. Approximately 3,500 subjects world-wide will be available for the efficacy evaluation of ABT-773. An estimated total of 5,300 subjects will be available for the safety evaluation of ABT-773 including Phase 1/2/3 data.

1. ABT-773 Dose Selection for Phase 2a Study in ABECB (M98-967)

ABT-773 is a potent antibacterial agent with *in-vitro* activity against community-acquired respiratory pathogens including S. pneumoniae, (including penicillin-resistant and macrolideresistant strains; PRSP and MRSP) H. influenzae, S. pyogenes, M. catarrhalis and atypical organisms including Mycoplasma spp., Chlamydia spp. and Legionella spp. It also has activity against anaerobic gram-positive bacteria found in the normal upper respiratory tract and the bowel flora.

In addition, ABT 773 has been shown to demonstrate *in vivo* efficacy in animal model pulmonary infection studies against these prevalent respiratory pathogens.

The highest MIC exhibited to ABT-773 among respiratory pathogens (including PRSP/MRSP) is that of *H. influenzae*. The MIC₉₀ ranges from 2-4 μ g/ml. In rat lung efficacy studies the CFU reduction in rat lung (2 log ₁₀ -3 log ₁₀) was exhibited by an AUC of 2.4-9.4 μ g•hr/ml when the drug was administered as a BID regimen.

Unformulated drug was delivered in capsules as QD, BID and TID regimens in dose-escalating single and multiple dose studies (100 mg QD as lowest dose) in order to evaluate the PK properties and safety profile, and to determine the dose regimen for the Phase 2a study.

The three key factors considered in selecting the dose and frequency of dosing for the Phase 2a study from the Phase 1 dose-escalating studies were; the AUC range necessary to treat *H. influenzae* in animal model studies, the safety profile of the drug, and the goal to simulate an extended release profile for eventual once daily dosing.

Based on these considerations 100 mg TID and 200 mg TID dose regimens were selected for Phase 2a study M98-967. The mean AUCs for these regimens determined in Phase 1 studies were approximately 4.1 µg•hr/ml and 14.9 µg•hr/ml, respectively.

2. Dose Selection for Phase 2b Studies ABECB (M98-048), ABS (M98-053) and CAP (M98-054) (M98-053)

In several Phase 1 studies the mean AUC for 300 mg QD (3 x 100 mg capsules) ranged from 4.8-8.0 µg•hr/ml. The mean AUC values for the QD regimen were higher in all four Phase 1 studies than for TID regimen, and additionally, in one Phase 1 cross-over study (5.9 vs. 4.1 µg•hr/ml) due to some extent of diurnal variation in absorption.

The efficacy/safety results of 100 mg TID (M98-967) were excellent. The clinical and bacteriological cure rates were both 98% and adverse events were low with the exception of 11% diarrhea. The study indicated that 100 mg TID is an effective dose in ABECB in terms of clinical and bacteriological outcomes and has an acceptable safety profile. Pharmacokinetic data from a subset of subjects in this study indicated that the mean AUC for this regimen was 5.5 µg•hr/ml. Based on these results, 300 mg QD was selected as the middle dose for the Phase 2b trials (a preferred regimen over a TID regimen for patience compliance) since the 100 mg TID had demonstrated acceptable efficacy/safety and the QD regimen provided greater exposure than the TID regimen (plasma mean AUC values of 4.1 and 5.9 µg•hr/ml, respectively) as discussed

above. In addition, the 300 mg dose administered QD had a mean C_{max} value of 0.9 µg/ml, which together with the exposure outlined above, provides adequate coverage for bactericidal activity against PRSP/MRSP with MIC₉₀ of 0.12.

Phase 2b studies were initiated with an immediate release tablet after multiple prototype extended release tablets failed to yield AUC values similar to that of the immediate release capsule and did not exhibit the desired extended release profile. Therefore, 150 mg immediate release tablets were manufactured and demonstrated to be bioequivalent to capsules (150 mg x 2 tablets vs 100 mg x 3 capsules) and were used in all three Phase 2b studies.

The 300 mg QD middle dose was bracketed in two of the dose-ranging Phase 2b studies (ABECB and ABS) with 150 mg and 600 mg doses to explore the optimal efficacy and safety range of the drug. In CAP, only 300 mg and 600 mg QD doses were used.

3. Dose Selection for Phase 3 Studies

The efficacy (clinical/bacteriology) data from the Phase 2b studies indicated that 150 mg, 300 mg and 600 mg were effective in treating subjects with ABECB (5 days) and ABS (10 days). The 300 mg and 600 mg were both effective doses to treat CAP (7 days) subjects.

The safety data indicated that all doses studied did not yield any clinically significant safety abnormalities as far as elevation of liver enzymes or QT prolongation are concerned. The 300 mg and 600 mg doses exhibited moderate amounts of taste disturbance and GI side effects, which were mainly diarrhea, nausea and vomiting.

Overall eradication of S. pneumoniae was excellent in all three studies. The data suggested that there was no apparent relationship between MIC and eradication or persistence of the isolates in the three trials, as would be expected with a susceptible population. There were no significant differences in eradication of S. pneumoniae between the dose groups in each of the trials and no evidence of development of resistance or of an increase in MIC in persistent isolates. Four MRSP isolates (2 mef/2 erm) were eradicated at the 150 mg dose in the ABECB study.

Regarding H. influenzae, overall eradication rates were high in ABECB and CAP. There were too few isolates in ABS to draw any conclusions. The data suggested that eradication or persistence was not predicted by the MIC value again consistent with a susceptible population where occasional persistent isolates are seen. Differences in eradication of *H. influenzae* were not significant between the dose groups in the three studies. For H. influenzae, 17/18 (94%) isolates were presumed eradicated in the ABECB study in the 150 mg arm of the study. The number of

H. influenzae isolates in the ABS study were too few to reach a meaningful conclusion (3/5) of presumed eradication.

There were no statistically significant differences between the 150 mg and 300 mg arms of the clinical outcome in ABECB and ABS studies, and the confidence intervals suggested they were equivalent in clinical outcome. However, 150 mg was tolerated better as far as taste disturbance and GI adverse events.

ABECB/Pharyngitis - Since both confidence intervals and statistical tests suggested that 150 mg and 300 mg dose groups were similar in both clinical and bacteriological outcome, it was decided to proceed into Phase 3 for ABECB indication with two studies using a 150 mg QD dose for 5 days. It was also decided to use this dose in the pharyngitis/tonsillitis studies, based on excellent *in vitro* activity of this drug against *S. pyogenes*, including macrolide resistant strains.

ABS - Excellent clinical activity was demonstrated in the 150 mg arm. Due to low pathogen recovery rate in this study, it was decided to conduct a double-blind Phase 3 two-dose study comparing 150 mg QD vs 150 mg BID (with sinus punctures) in lieu of the open single dose Phase 3 study as recommended in the FDA guidance document. After selecting the most appropriate dose from this initial study, based on clinical efficacy/bacteriology and safety outcomes, two additional Phase 3 pivotal studies will be performed. For this first study, 150 mg BID was selected since this regimen has been shown to have a lower C max compared to 300 mg QD, thus potentially resulting in less taste disturbance and possibly lower GI side effects. In addition, the AUC values (3.9-5.8) obtained in Phase 1 studies are within AUC values of 150 mg and 300 mg QD, two doses that were shown to be effective in this indication.

<u>CAP</u> – For this indication, it was decided to conduct a double-blind Phase 3 two-dose study comparing 150 mg QD vs 150 mg BID in lieu of the open single dose Phase 3 study as recommended in the guidance document. The 150 mg QD dose was included, although it was not evaluated in the Phase 2b study, it exhibited efficacy in the ABECB and ABS Phase 2b studies. The 150 mg BID was selected due to its potentially lower taste disturbance and GI adverse event profile compared to 300 mg QD. After selecting the most appropriate dose from this initial study, based on clinical efficacy/bacteriology and safety outcomes, two additional Phase 3 pivotal studies will be performed.

4. Selection of comparators for Phase III studies

Selection of comparators were based on input from PPD, AI and affiliate marketing groups, medical and regulatory members of PPD and AI and finally input from three regulatory agencies

in Europe (UK, France and Germany) as well as US FDA Anti-Infective Division. A total of 10 studies are planned to be conducted. Two studies in ABECB, one in Europe and one in US. The European study will be vs Levofloxacin and US study vs Azithromycin. Both drugs have major market shares in this indication, Azithromycin in US and Levofloxacin is gaining momentum in Europe.

There are three planned studies for ABS, including two comparative studies vs Augmentin. And the two dose ABT 773 study. Augmentin is a key product in this indication both in US and Europe. In all probability, for the European study, Augmentin will be replaced with a quinolone. The plan will be finalized shortly.

The plan for acute streptococcal pharyngitis (ASP) calls for two studies against the standard treatment; Penicillin V. 500mg tid, one in US and the second in Europe.

The CAP plan calls for three studies, the first, a two dose study of ABT 773 followed by a comparative study in Europe vs Augmentin and a comparative study in US vs Levofloxacin. Both products are used in this indication and it will be important to compare the efficacy/safety profile of ABT 773 with these agents. In all probability, for the European study, Augmentin will be replaced with a Amoxicillin 1gm TID. The plan will be finalized shortly

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H. Chemistry, Manufacturing and Controls

Chemistry, Manufacturing and Controls SWOT Analysis H.1

	Table II.1 SWOT analysis (Strengths/Weaknesses/Opportunities/Threats)				
CATEGORY	ITEM (Probability/Impact)	STRATEGY			
Strengths	Over 3600 kg of bulk drug have been successfully manufactured with overall yields improving from 21% to greater than 30%. Excellent progress on improving costs of bulk drug, currently less than S6500/kg with target of \$2500/kg at launch	Produce required development quantities of bulk drug to meet the cost targets at launch. Continue to obtain yield improvements through process work and manufacturing volume. Obtain Regulatory approval (both AI and FDA) to identify intermediate step 5 as a starting material to allow for further process improvements at the earlier steps of manufacturing.			
	Registration runs incorporated qualifying vendors for intermediates that will drive further bulk drug cost reductions and assure availablity of bulk drug.	Continue to decrease cost of intermediates through use of three to four vendors.			
	Formulation is a familiar technology, immediate release QD formulation manufactured by wet granulation.	Utilize an integrated scale-up program with both PARD and IDC to assure that a single formula/process will be used worldwide.			
	Two sites of final product manufacturing (one in the U.S. and one in AI) at launch.	Two manufacturing sites provides back up support to AI and future potential back up to the U.S.			
Weaknesses	Current bulk drug process requires 9 steps and high cost side chain which may limit potential cost improvements beyond launch. ABT-773 has a bitter after taste as a result of	Process development underway to evaluate optimized/new chemistry routes and potential to simplify the manufacturing process.			
	excretion into the saliva that cannot be masked in the formulation. This is the most frequent adverse event identified in the Phase II clinicals.	The 150 mg tablet minimizes after taste problems however, this will be a challenge in formulating a pediatric product			
	Phase III clinicals and NDA stability will be performed using an intermediate scale formulation.	A bioequivalency study will be performed linking the 10L bench formulation used in the Phase II clinicals, to the 300L intermediate formulation used in the Phase III clinicals, to the commercial scale (1200L U.S. and 600L U.K.) formulations.			
	Due to Regulatory issues, there will not be a back-up site for the U.S. at launch.	Evaluate a separate project to obtain second site approval for the AI site to provide back up to the U.S.			
Opportunities	Experience with bulk drug substance in terms of physical properties will allow us to develop specifications to improve consistency in formulation.	Particle size analysis is ongoing to provide data to support defining physical specifications by January 2001.			

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	Obtaining regulatory approval for definition of step 5 as starting material will provide more opportunity for process improvements to reduce COGs	SPD, PPD and Al are collaborating ona solida data package to detend our step 5 starting material definition. An end of Phase II CMC meeting will be scheduled at the end of 200 with FDA to discuss our strategy. Early discussions with the U.K. regulatory agency were optimistic.
Threats	Having one site for bulk drug can always carry risks.	A second site (Puerto Rico or Italy) will be considered in 2001 based on marketing forecast and capacity.

H.2 **SPD/PPD Chemical Sciences**

SPD has made significant breakthroughs since 1997 to bring the cost of drug from S30M to \$6.5M. Further reductions are expected by reducing the cost of the PQC side chain (competitive bidding among vendors), reducing the number of process steps, reducing the number of intermediate isolations, and increasing the batch size. An ongoing analysis of the assembly process is being made to evaluate the efficiencies gained in various steps in the process, and/or outsourcing a series of steps. The cost of drug during the filing year, 2002 is anticipated to be about \$2500/Kg.

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4:

Bulk Drug Requirement

Project: ABT-773 Adult Tablet Inventory Balance 964kg End Q4 1999 Bulk Deliveries Usage (Quantity) Description Clinical Fermulation Quantity Scale-Up Inventory 1285.2kg Q1 2000 Campaign 6, pre-NDA run 321.2kg 321.2 kg Q2 2000 | Campaign 7, 8, 9 NDA runs 2294.1 1008.9 kg1008.9 kg1029.9 kg 3324kg Q3 2000 Campaign 10, NDA run, Cam 11,12 1029.9 kg dev runs Q4 2000 Campaigns 13, 14 development runs 670 kg 670 kg 3994kg Campaign 15, 16 development runs Q1 2001 670 kg 670 kg 4664kg $\mathrm{Q}2\ 2001$ Shut down for facility upgrade 4664kg Q3 2001 | Campaign 17 335 kg 335 kg 4999kg 670 kg 670 kg 5669kg Q4 2001 Campaign 18.19

Lead Time (request to delivery; weeks)

Comments:

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Schedule B ABT-773 Bulk Drug Usage – Tablet Formulation

Task	Start	Finish	Task Use
1 10L Formulation Prototypes	Nov/09/98	Jun/30/99	107.8
12 75L Process Dev't/Bulk Drug Eval (24 runs, 200 kg)	Aug/23/99	Oct/01/99	151.0
Clinical Re-Supply PH II	Sep/08/99	Sep/08/99	5.4
14 Dissoln Method Justification Biostudy- Clin Mfg - 3 runs	Oct/04/99	Nov/15/99	24.0
16 Process Dev/Bulk Drug Eval 75L Pt2 (8 runs, 66.4 kg)	Nov/16/99	Dec/10/99	59.0
 UK Site/2nd Process Verification 25L (33 kg) Batches 1-3 Batches 4-6 Batches 7-10 (two batches) 	Dec/01/99 Feb/01/00 Mar/14/00	Jan/31/00 Mar/13/00 Oct/11/00	10.0 10.0 13.2
22 Proc. Supportive Dev, 75L Pt3 (16 runs-rep. Scale; 132.8kg)	Dec/13/99	Feb/04/00	132.8
24 75 L Bulk Drug Eval Pt 3 (10 runs; INCL cmpn 6 re-work)	Feb/01/00	Dec/01/00	84.7
26 Process Dev 300L (4 runs; 133.2 kg)	Jan/10/00	Feb/04/00	130.0
Phase III Clin Supply mfg, 75L Gral, 300 mg white, 62-329-AR 75L, 200 mg IR-D, lot 65-362-AR	Mar/14/00 May/22/2000	Mar/21/00 Jul/14/2000	16.1 24.1
28 Process Dev Pre-NDA (11 runs; 366.3 kg) 300L Gral, 300 mg IR-D ScaleUp Lot; 65-015-4Q	Feb/07/00 May/31/2000	Apr/14/00 Jun/13/200 0	364.0 64.2
150 mg switch 150 mg factorial compression study 150 mg tablet coating study			24.0 56.0
33 Mfg. NDA Runs - 1 Strength (4 lots/10 runs; 333kg) 34 NDA Lot 1 (Abbott; Cmpgn 7-rework)	7	Jul/17/00	66.6
NDA Bio Lot 2 (ChemiSpa), Phase III supplies; 66-018-4Q	: Jul/31/00	Aug/11/00	66.6
NDA Lot 3 (Uquifa): 67-021-4Q	Sep/25/00	Oct/06/00	66.6
NDA Lot 4 (Taisho)	Sep/25/00	Oct/06/00	66.6
39 Process Verification 65 L (146 kg)	Feb/07/00	Sep/29/00	
Batches 1-6	Oct/18/00	May/31/00	50.0
Batches 7-12	Jun/01/00	Jul/31/00	50.0
Batches 12-15 (two batches)	Aug/01/00	Mar/26/01	35.0
Biobatch, 65L vs 300L (20 kg)	May/01/01	May/31/01	20.0
46 Process Dev 1200 L (4 runs, 532 kg) +1 run?= 665kg	Jan/22/01	Mar/05/01	665.0

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	50
50 1200L Def Bio & Registration Lots (3 lots, 4 runs; 532 kg) Mar/06/01 Jul/09/0	1 532.0
Definitive Biostudy, 300L vs 1200L May/29/01 Jun/25/0)1
57 75L Supportive Dev (For the 1200L, 20 runs; 166 kg) Jan/17/01 Aug/23/0	01 166.2
58 300L Supportive Dev (For the 1200L, 5 runs; 166.5 kg) Jan/17/01 Aug/23/0	01 167.0
60 Demonstration Lot 1200 L (3 runs; 399 kg) Apr/01/02 ? Jun/21/0	02 399.0
65 Process Transfer(i) 600L U.K. Site (3X 83 kg= 249kg) Apr/19/01 May/18/	01 249.0
Process Transfer (ii) 600L U.K. (2x 83kg= 166 kg) Jun/27/01 Jul/24/0	1 166.0
Bio Batch UK Sep/13/01 Oct/02/0	01 83.0
Batch Analysis, 2 lots; 2x 83 kg Sep/05/01 Sept/27/	01 166.0
Demo Batch 1 UK; (1 lot, 3 runs= 333 kg) Apr/04/02 May/03/	02 333.0
1200L Validation Runs (3 Lots, 3 Runs ea; 1197 kg) Jun/05/02 Aug/28/0	02 1200.0
Launch 1Q2003	
Total Bulk Drug Usage	5823.90

Schedule C

Bulk Drug Cost Status

	Current Average Cost (000)	Projected Commercial Cost (000)
Materials	3.7	1.3
Labor/Equipment	2.4	1.05
Process Support	0.4	.15
Total	6.5	2.5

	_	Project Av	Average Cost/Kilo		
Event	Year	DDC	Actual/Project	Projected	
DDC	97	150	150		
	98	30	30	Λ	
Phase IIb	99	10	10	Α	
Phase III start	00	7.5	6.7	A	
	01	5.0	5.0	P	
Filing	02	4.0	4.0	P	
Launch	03	2.5	2.5	P	
Dose Projection		150mg/Day	150mg/Day		
Cost/Dose/Day Bottle		\$0.4218/Day	\$0.4218/Day		
Cost/Dose/Day Blister		\$0.5702/Day	\$0.5702/Day		

II.3 PARD/IDC

An immediate release 150 mg formulation has been selected for commercial development of ABT 773. The formulation was reduced in size from the original 300 mg tablet previously targeted for development. The formula and process will be global with respect the excipients and an integrated scale up program with the IDC will assure that a single formula/process (with common packages) will be used throughout the world. The CMC working group continues to review needs on the bulk drug for clinical use and process development as the program develops. Common specifications for the bulk drug substance and the formulation remain a goal of the CMC development group.

Document 362-5

H.4 Manufacturing

ABT-773 tablets will be manufactured in AP16 for PPD domestic supply, and as a back-up facility for AI supply. Queenborough, UK will manufacture for AI supply, including Japan. There will be a common, global formula (0.3g tablet weight, with pale pink coating). The only possible exception will be if we need to develop different codes of bulk drug for PPD and AI.

The manufacturing process is a conventional tableting process. In AP16, ABT-773 will be granulated in the 1200L Gral, in 3 runs, then blended (75 cuft), compressed and coated (60" Accelacoater) as 150mg tablets. In the UK, ABT-773 will be granulated in the 600L TK Fielder, in the 3 runs, then blended and coated as 150mg tablets. The Japanese product will be manufactured with the same granule, to a lower compression weight, if Japan proceeds with 100mg tablets. This strength is yet to be determined. Capacity reviews at both plants indicate that there is sufficient capacity, including upside demand. The tablets will be packaged into 30# bottles, and peelable blister (Hospital Unit Dose) and push-through blister (compliance pac)

H.5 Patent Issues

U.S. Patent 5,866,549 claiming ABT-773 and its analogs issued on February 2, 1999. The patent will expire on September 4, 2016. Three divisional applications claiming related compounds in the series are pending prosecution in the United States Patent and Trademark Office. The patent applications corresponding to the issued patent and pending patent applications have been filed in more than forty countries outside the US, thus providing extensive worldwide patent protection for the compound

I. Non-Clinical

I,1 Non-Clinical SWOT Analysis

Strengths, weakness, opportunities and threats regarding the non-clinical program for ABT-773 are discussed below:

Table I.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)					
CATEGORY	ITEM (Probability/Impact)	STRATEGY			
Strengths	All key toxicology studies have been initiated or completed.	Complete Tox package for NDA early on.			
	ABT-773 is active against penicillin- resistant and macrolide-resistant <i>S.</i> pneumoniae including Erm AM and Mcf phenotypes; it does not induce MLS _b (macrolides, lincosamides and streptogramin B) resistance.	Key positioning in the marketplace as a safe, effective antibiotic that treats resistant organisms and does not induce resistance.			
Weaknesses	Tox: Relatively small safety margins between the no-effect level exposures and clinical exposure.	Safety data is available from clinical studies.			
	Micro: Pharmacokinetic profile based on traditional profiles, may not support the 150mg dose.	Ribosome kinetics are now being studied as a means of providing crucial support to our decision to proceed with 150 mg. A plan has been established to devise a mechanistic rationale for the 150 mg program that goes beyond the traditional two-factor paradigm i.e. concentration & MIC and establishes this concept as the new in vitro paradigm to predict efficacy.			
	H. Flu MIC 2-4 is a high MIC to achieve by blood levels.	Demonstrate clinical activity in <i>H. flu</i> and use tissue level data if available.			
Opportunities	Micro: Kinetic and binding studies have shown that this ketolide associates very rapidly with susceptible ribosomes and dissociates very slowly. ABT-773 also appears to be capable of lower affinity binding for methylated streptococcal ribosomes	Further characterization of this additional binding and its role in antibacterial activity is being investigated.			
Threats	Testicular effects and impaired fertility in the rat Segment I study.	Fertility evaluation should be included in the clinical program.			

All key toxicology studies for ABT-773 have been initiated or completed. All acute and genetic toxicity studies, two-week toxicity studies in rat and monkey, one-month toxicity studies in rat and monkey, a three-month study in rat, and embryonic and fetal developmental (Segment II) studies have been completed. A three-month study in monkey, a juvenile toxicity study in rat, a fertility and early embryonic development (Segment I) study in rat, a peri- and postnatal (Segment III) study in rat and an antigenicity study in guinea pig are ongoing.

In rats, increased mortality, decreased body weight gain and food consumption, and manifestations of toxicity in the liver, kidney, lung, testes and epididymides were observed at dosages of 180 and 160 mg/kg/day in the one-month and three-month study, respectively. Mild and reversible toxicity of these organ systems was seen at 60 mg/kg/day. The no-toxic-effect level (NTEL) in the three-month rat study was 20 mg/kg/day (AUC = 11-25 μ g•hr/ml). The mean plasma exposure of ABT-773 in humans is expected to be 2-5 μ g•hr/ml (150-300 mg/day dose) and thus the NTEL in animals are approximately 2-13 times higher than anticipated human exposures.

In monkeys, emesis was observed in a dose-related manner. Decreased body weight gain and food consumption, and manifestations of toxicity in the liver, kidney, bone marrow and lymphoid tissues were observed at a dosage of 200/140 mg/kg/day in the one-month study. Preliminary data showed that liver toxicity was also observed at dosages of 50 and 100 mg/kg/day in the three-month study. The no-toxic-effect level (NTEL) in the three-month monkey study was 25 mg/kg/day (AUC = 7-10 μ g-hr/ml); exposures at this dosage are approximately 1.5-5 times higher than anticipated human exposures.

Embryonic and fetal developmental studies conducted showed no fetal malformation at dosages up to 80 mg/kg/day in rats and 100 mg/kg/day in rabbits. In an ongoing fertility and early embryonic development study, preliminary data showed adverse effects on fertility at dosages of 60 and 180 mg/kg/day. Recovery of this effect on fertility was seen at 60 mg/kg/day, but not at 180 mg/kg/day. This finding agrees with the testicular effects seen in the three-month rat study. Clinical implications of this finding is not known, although similar findings have been reported with other macrolides. Preliminary data of the peri- and postnatal study showed decreased pup growth and development at 80 mg/kg/day; these effects were believed to be secondary to reduced weight gain of dams during gestation.

Genetic toxicology studies conducted with ABT-773 included Ames assay, mouse lymphoma assay, *in vitro* cytogenetics assay and *in vivo* mouse micronucleus assay. ABT-773 was not found to be genotoxic in any of these assays.

New impurities, not covered by the toxicology lot used for three-month studies, have been generated. Acute toxicity, genotoxicity and bioavailability studies are being conducted with these impurities to qualify their use in the clinical trials. Longer term toxicology testing will be done when the impurity profile for ABT-773 is determined (NDA runs).

1.3 Metabolism

Studies of the oral or intravenous single dose pharmacokinetics of ABT-773 have been performed in the rat, mouse, dog and monkey following single doses. These data suggested ABT-773 may possess a balanced pharmacokinetic profile similar to that of clarithromycin. ABT-773 exhibits sufficient plasma concentrations and tissue distribution to provide effective treatment *in vivo* for bacterial infections of upper and lower respiratory tract. The data from the study in dogs indicate that ABT-773 has a favorable oral pharmacokinetic profile with 51.3% absolute bioavailability from a simple capsule formulation and low animal-to-animal variability. ABT-773 has a half-life similar to that of clarithromycin in dogs (4.1 and 5.4 hrs, respectively), with a C_{max} of $0.88~\mu g/mL$ following an oral dose of 5 mg/kg.

[¹⁴C] ABT-773 was found to undergo NADPII-dependent metabolism by liver microsomes from mouse, rat, dog, monkey and humans with wide interspecies variability in the rates of metabolism with monkey and rat exhibiting highest and lowest rates of metabolism, respectively. In all cases the major metabolite formed was an *N*-desmethyl derivative of ABT-773 (M-1). ABT-773 is rapidly cleared in rats after intravenous and oral administration and in dogs by oral administration. For both species, excretion is primarily by the liver with only a small fraction of the dose eliminated in the urine.

The *in vitro* studies across five species including man, suggest that ABT-773 shows a drug-concentration dependent decrease in protein binding. In man, for plasma concentrations above 3 mg/mL, plasma protein binding decreases with increasing total drug concentrations, presumably due to the saturation of the plasma binding sites. Because plasma concentrations of ABT-773 in humans are unlikely to exceed 2 mg/mL at clinically-relevant doses, the concentration dependence is not clinically important. In human plasma, [14 C] ABT-773 has a greater affinity for α_1 -acid glycoprotein (AAG) than for human scrum albumin (HSA), and plasma protein binding at concentrations of 0.1 to 3 µg/mL was 95.5-95.6%.

Filed 03/10/2008

ABT-773 is metabolized by human liver microsomes via CYP3A4. The drug also appears to be an inhibitor of CYP3A4 metabolism in vitro. The IC_v values obtained for the inhibition of CYP3A4-dependent metabolisms were in the same range as the total steady state peak plasma concentrations of ABT-773 (0.45 - 1.92 µg/mL) after 200-500 mg BID doses in humans. This indicates the potential for ABT-773 to inhibit the *in vivo* metabolism of coadministered drugs metabolized via CYP3A4

I.4 Animal Safety Pharmacology

The pharmacology studies showed that ABT-773 has mild sedative actions with only modest, if any effects on other CNS, CV and/or GI functions at the rapeutic to super the rapeutic doses/plasma concentrations. These results indicate a minimal risk for marked adverse effects of this compound in clinical studies

In in vitro cellular electrophysiologic studies, supratherapeutic concentrations of ABT-773 (at concentrations 10- and 100-fold above anticipated clinical therapeutic plasma levels) prolong the action potential duration of canine cardiac Purkinje fibers superfused with physiologic salt solutions. These in vitro studies likely overestimate the electrophysiologic effects of ABT-773 in vivo due to the extensive plasma protein binding of ABT-773. Prolongation of the Purkinje fiber action potential duration in vitro is dramatically reduced in the presence of plasma proteins; in the presence of 50% plasma, the dose-response curve for prolongation is shifted rightward, with significant prolongation observed only at 100-fold above the anticipated plasma levels of ABT-773.

When studied in the absence of plasma, the extent of action potential prolongation with ABT-773 is comparable to erythromycin, clarithromycin, and levofloxacin, and less than that of moxifloxacin when compared on the basis of plasma concentration multiples. Studies of M-1, the principal metabolite of ABT-773, demonstrate minimal effects on repolarization and only at high metabolite concentrations (100-fold excess of those found at clinically efficacious concentrations). An in vivo toxicology study with non-human primates reveals no significant prolongation of the QTe interval despite long-term exposure to supratherapeutic plasma levels of ABT-773.

1.5 Microbiology

In the past year, various external investigators have confirmed and expanded the early preclinical studies done at Abbott. The activity of ABT-773 against current respiratory tract

isolates including *S. pneumoniae* (macrolide susceptible and resistant), *H. influenzae* and *M. catarrhalis* was examined. An antibiotic surveillance study done by the University of Iowa found the MIC₅₀ of ABT-773 for *S. pneumoniae* (n=1601) was 0.03 μg/ml. Furthermore, the MIC₅₀ against low and high level macrolide resistant strains was 0.12 μg/ml. The highest ABT-773 MIC found in the study was 0.5 μg/ml (n=3). The activity of ABT-773 was found to be equivalent to azithromycin and superior to clarithromycin against *H. influenzae* and the ketolide was extremely potent against *M. catarrhalis*. Additional studies done by several other investigators confirmed these findings for respiratory pathogens. Kill kinetic studies with fastidious respiratory pathogens confirmed the bactericidal activity of ABT-773. The ketolide also showed extended post antibiotic effect compared to other macrolides for *S. pneumoniae* and *H. influenzae*.

Kinetic and binding studies have shown that this ketolide associates very rapidly with susceptible ribosomes and dissociates very slowly. ABT-773 also appears to be capable of lower affinity binding for methylated streptococcal ribosomes. Further characterization of this additional binding and its role in anti-bacterial activity is being investigated.

ABT-773 demonstrates *in vivo* efficacy equal or superior to available clinical therapeutics in animal studies against the most prevalent respiratory pathogens including *Streptococcus* pneumoniae and *Haemophilus influenzae*. Once daily (QD) therapy was as effective as twice daily (BID) therapy in treatment of rat pulmonary infections caused by *H. influenzae* and *S. pneumoniae*. ABT-773 also demonstrated efficacy against macrolide and penicillin resistant strains of *Streptococcus pneumoniae*. Efficacy was demonstrated against infections of salient anatomical locations including systemic (septic), inner ear (bullae), pulmonary, and skin abscess suggesting that ABT-773 penetrates into pulmonary tissue and intracellular locations while maintaining activity.

Addenda

- 1.0 **Target Product Label**
- 2.0 Clinical Trial Program
 - 2.1 **Clinical Trials (Gantt Chart)**
- 3.0 Chemistry, Manufacturing and Controls
 - Milestones SPD/PPD Chemical Sciences Milestones (Gantt Chart) 3.1
 - 3.2 PARD Milestones (Gantt Chart)
- 4.0 Non-Clinical
 - 4.1 Animal Toxicology and Metabolism Milestones (Gantt Chart)
- 5.0 **Project History**
 - 5.1 **Expert Strategic Review Process - Summaries**
 - 5.2 Milestones
 - 5.3 Highlights re: NCE
 - 5.4 Historical Changes to ABT-XXX Target Product Profile

Appendix 1

Target Product Label

ERADICATE® Filmtab®

(eradomycin tablets)

DESCRIPTION

Eradomycin is a semi-synthetic ketolide antibiotic. Chemically, it is 11-amino-11-deoxy-3-oxo-5-O-desosaminyl-6-O-[3'-(3"-quinolinyl)-2'-propenyl] erythronolide¹ A 11,12-cyclic carbamate. The molecular formula is $C_{42}II_{59}N_3O_{10}$, and the molecular weight is 765.94². The structural formula is:

ERADOMYCIN is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol,

ethanol, and acetonitrile, and practically insoluble in water³.

ERADOMYCIN is available as immediate release tablets.

Each ovaloid film-coated ABT-773 tablet contains 150 mg of ABT-773 and the following inactive ingredients: Cellulose, Microcrystalline, NF Croscarmellose, Sodium, NF Hydroxypropyl Cellulose NF Magnesium Stearate, NF, Impalpable Powder Silicon Dioxide, Colloidal, NF Sodium Starch Glycolate, NF Powder Starch, Pregelatinized, NF

Plus- coating solution (STILL BEING DEFINED):

iron oxides, hydroxypropyl methylcellulose, Polyethylene Glycol, Titanium Dioxide, sorbic acid?⁴.

Study# C	omment	<u>Start</u>	<u>End</u>	Investigator/Contact
¹ NA	Confirm chemical name (IUPAC)			Z. Ma
2 NA	Confirmed			Z. Ma
³ NA	Confirmed			Z. Ma
⁴ NA	Info correct, how specific is required?			R. Schilling

CLINICAL PHARMACOLOGY

ERADOMYCIN is rapidly absorbed from the gastrointestinal tract after oral administration⁵. The absolute bioavailability of 150-mg ERADOMYCIN tablets was approximately ??% ⁶⁻⁷⁻⁸. Food effects neither the rate nor extent of ERADOMYCIN absorption. Therefore, ERADOMYCIN tablets may be given without regard to food9.

In fasting healthy human subjects, peak serum concentrations were attained within 3 hours after oral dosing 10-11. Steady-state peak serum ERADOMYCIN concentrations were attained in 3 to 4 days¹² and were approximately 1 ug/mL¹³ with a 150-mg dose administered every 24 hours. The pharmacokinetics of ERADOMYCIN are nonlinear around the recommended dose of 150 mg administered once daily^{14–15}. Typical pharmacokinetic parameters of ERADOMYCIN are shown in the following table.

Error! Bookmark not defined.PHARMACOKINETIC PARAMETERS

		(after 150 mg q 2 4 h	1)	
_	T _{max} 16 (h)	T _{1/2} ¹⁷ (h)	C _{max} ¹⁸ (ng/ml)	C _{min} 19 (ng/ml)	AUC^{20}
					(ng·h/ml)
_	2.7 ± 0.6		855 <u>+</u> 366	29 <u>+</u> 13	5934 <u>+</u> 2623

After a 150-mg tablet every 24 hours, approximately ?%²¹ of the dose is excreted in the urine as ERADOMYCIN. [No metabolite info presented; may have to defend]. [Does CYP3A have to be mentioned?] . The elimination halflife of ERADOMYCIN was about 6 to 8 hours²² with 150 mg administered every 24 hours.

The steady-state concentrations of ERADOMYCIN in subjects with impaired hepatic function did not differ from those in normal subjects²³; the steady-state concentrations of ERADOMYCIN in subjects with impaired renal function did not differ from those in normal subjects²⁴. [Will conduct study in elderly²⁵; will add comments about

⁵ <u>M00-AAA</u>	Definitive biostudy
⁶ М00-БВЕ	Single ascending IV, final, multiple rising dose + p.o.; assumes
7	p.o. does not have to be final scale for 8/00 start.
100027	
8 <u>100098</u>	
⁹ <u>M00-AAA</u>	To be part of definitive biostudy
¹⁰ М97-716	3 hrs based on 716
11 <u>M00-AAA</u>	Confirmed with definitive biostudy
¹² <u>M99-024</u>	3-4 days based on 024 study; repeat only if diff. between
1.3	024 and 10-75L scaleup (<u>M99-129</u>)
¹³ <u>M99-014</u>	024 showed 1 mge/ml; repeat only if diff, between
14	024 and 10-75L scalcup (<u>M99-129</u>)
¹⁴ <u>M99-018</u>	Quantify non-linearity from study
¹⁵ M00-CCC	150/300/600 mg single comparative study
1.6	If done, 018 would not be used; could also use M99-119 caucasian section
¹⁶ <u>M99-016</u>	Placeholder study; replace with M00-AAA
¹⁷ <u>М99-016</u>	Placeholder study; replace with M00-AAA
¹⁸ <u>M99-016</u>	Placeholder study, replace with M00-AAA
¹⁹ <u>M99-016</u>	Placeholder study, replace with M00-AAA
²⁰ <u>M99-016</u>	Placeholder study; replace with M00-AAA
²¹ M00-DDD	C14 study, if low number (<20%), multiple dose
	will not be required
²² M99-024	6-8 hours based on 024 study; will also be based on M00-AAA
²³ <u>M99-126</u>	Protocol finished
²⁴ M00-FFF	Low urine excretion will not require results of C14;
²⁵ <u>M01-AAA</u>	Study in alderly; need final desage form/dese

gender subanalyses but no specific studies]

Do we need adolescent study/section in tabel?

Distribution:

ERADOMYCIN distributes readily into body tissues and fluids. Volume of distribution?²⁶ Rapid distribution of eradomycin into tissues results in higher eradomycin concentrations in most target tissues than in serum (see table below) [will use either tissue and serum values or only ratios, whichever looks more favorable].

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(after 150 mg q 24 h)			
	Tissue	Serum	T:S Ratio
Tissue Type	(μg/g)	(µg/mL)	(µg/mL)
Tonsil ²⁷	X.X	X.X	X.X
Lung ²⁸⁻²⁹	X.X	X.X	X.X
Epithelial Lining Fluid ³⁰⁻³¹	X.X	X.X	X.X
Alveolar Macrophage ³²⁻³³	X.X	X.X	X.X
White Blood Cells ³⁴	X.X	X.X	X.X
Sinus Mucosa ³⁵	X.X	X.X	X.X
Cerebral Spinal Fluid ³⁶	X.X	X.X	X.X
Bronchial Mucosa ³⁷	X.X	X.X	X.X
Sputum ³⁸	X.X	X.X	X.X

 $^{26} \rm M00\text{-}BBB$ Absolute bioavailability study 27<u>M99-142</u> Conte study; all raw data must be sent to Abbott, will forward to FDA (10009)²⁸<u>M99-142</u> ²⁹M99-007 Gottfried to execute; contact Gottfried for proposal ³⁰<u>M99-142</u> Conte study 31<u>M99-007</u> 32<u>M92-142</u> Conte study ³³<u>M99-007</u> 34<u>M99-105</u> 35 Samples being reassayed, orig. results relatively low TBD; not sure if pursuing 36<u>M99-142</u> 37 Conte study TBD; not sure if pursuing 38 TBD; not sure if pursuing, ELF is better fluid

Microbiology:

ERADOMYCIN is a ketolide with concentration-dependent, bactericidal in-vitro activity against a wide range of aerobic and anaerobic gram-negative, gram-positive, and atypical microorganisms. ERADOMYCIN exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of bacterial protein synthesis 39-40-41-42. ABT-773 binds to the ribosome rapidly, completely, and irreversibly 43. It appears that these ribosome-binding properties contribute to enhanced activity and lower selection of resistant mutants of gram-positive bacteria relative to other agents that act via the ribosome 44 45 46 Eradomycin exhibits an in-vitro post-antibiotic effect (PAE), defined as the ability of an agent to sustain antimic robial action after drug concentrations have fallen below the MIC. $^{\!\! 8}$

The mechanism of action of ketolides including eradomycin is different from that of penicillins, cephalosporins, quinolones, aminoglycosides, and tetracyclines⁵¹. Therefore, **ERADOMYCIN** may be active against pathogens that are resistant to these antibiotics^{52–53–54–55}. There is no cross-resistance between **ERADOMYCIN** and the mentioned classes of antibiotics⁵⁶.

Macrolide resistance occurs principally by two main mechanisms of resistance. Production of ribosomal methylases, either inducible or constitutive, alters the ribosomal target inhibiting macrolide binding; an efflux mechanism pumps the antibiotic from within the microorganism. ERADOMYCIN has been shown in streptococcus to bind to methylated ribosomes^{57 58}, to not induce methylase resistance^{59 60}, and to bypass the efflux pump⁶¹⁻⁶². Thus ERADOMYCIN is active against macrolide resistant streptococci⁶³⁻⁶¹⁻⁶.

Resistance to ERADOMYCIN in vitro develops slowly66. Resistance to ERADOMYCIN in vitro occurs at a

³⁹ 99040	Capobianeo
⁴⁰ 99017	Zhong
⁴¹ 99032	Zhong
$^{42}100077$	Zhong
⁴³ 99040	-
⁴⁴ 99068	Liebowitz study (serial dilution)
$\frac{45}{100079}$	Nilius, will be at ICAAC00
$\frac{46}{100027}$	Pendland
⁴⁷ 100048	
48 ₉₉₀₀₁	Appelbaum; partial ICAAC99, ICAAC00
49 100078	Ramer
⁵⁰ 99014	Dubois
51	Scientifically accepted; provide literature references
⁵² 99051	,
⁵³ 99030	
⁵⁴ 99038	
55 99042	
56	99051, 99030, 99038, 99042
⁵⁷ 99040	Zhong mechanism of action reference
⁵⁸ 99071	Mankin
⁵⁹ 99040	
60 99038	Shortridge
61 ₉₉₀₄₀	
62 ₉₉₀₃₈	
63 ₉₉₀₃₈	Multiple in-vitro studies
64 ₉₉₀₅₁	•
65 ₉₉₀₃₀	
GG	99068, 100027, 100079

general frequency of between 1 x 10° to 10°.

ERADOMYCIN has been shown to be active against most strains of the following microorganisms both in-vitro and in clinical infections as described in the INDICATIONS AND USAGE section:

Aerobic Gram-Positive Microorganisms

Staphylococcus aureus (methicillin-susceptible strains; macrolide inducibly resistant and efflux strains) Staphylococcus epidermidis (methicillin-susceptible strains)

Streptococcus pneumoniae (including penicillin-susceptible, intermediate and resistant strains; macrolide susceptible, intermediate and resistant strains; quinolone susceptible, intermediate and resistant strains) Streptococcus pyogenes including macrolide susceptible, intermediate and resistant strains;

Aerobic Gram-Negative Microorganisms

Haemophilus influenzae (including beta-lactamase producing strains and beta-lactamase negative ampicillin resistant (BLNAR) strains)

Haemophilus parainfluenzae (including beta-lactamase producing strains) Moraxella catarrhalis (including beta-lactamase producing strains)

Other Microorganisms

Mycoplasma pneumoniae Chlamydia pneumoniae (TWAR) Legionella pneumophila

The following in vitro data are available, but their clinical significance is unknown.

Eradomycin exhibits in-vitro minimum inhibitory concentrations (MICs) of ≤2 µg/ml against most (≥90%) strains of the following bacteria; however, the safety and effectiveness of eradomycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive Microorganisms

Streptococcus agalactiae Streptococci (Groups C, F, G) Coagulase negative staphylocooci (methicillin suceptible) Viridans group streptococci

Corynebacterium jeikeium

Corynebacterium spp.

Listeria monocytogenes

67 99068, 100027, 100079

Aerobic Gram-negative Microorganisms

Bordetella pertussis

Legionella pneumophila Neisseria meningitidis

Neisseria gonorrhoeae (including penicillin resistant and quinolone resistant strains)

Anaerobic Gram-positive Microorganisms

Peptostreptocococi

Propionibacterium acnes Clostridium difficile Clostridium perfringens

Anaerobic Gram-negative Microorganisms

Bacteriodes spp. Porphyromonas spp. Prevotella spp.

Dilution Techniques

Quantitative methods that are used to determine minimum inhibitory concentrations (MICs) provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of eradomycin powder. The MIC values obtained should be interpreted according to the following criteria:

For testing non-fastidious aerobic organisms

MIC (μg/mL)	Interpretation
≤2.0	Susceptible (S)
4.0	Intermediate (I)
>8.0	Resistant (R)

For testing Haemophilus spp.*

MIC (μg/mL)	Interpretation
≤4.0	Susceptible (S)
8.0	Intermediate (I)
≥16.0	Resistant (R)

This interpretive standard is applicable only to broth microdilution susceptibility tests with Haemophilus spp. using Haemophilus Test Medium (HTM).1

For testing Streptococcus spp. including Streptococcus pneumoniae b

MIC (mcg/mL)	Interpretation
--------------	----------------

<u>≤</u> 0.5	Susceptible (S)
1.0	Intermediate (I)
<u>>2</u> .0	Resistant (R)

b These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.¹

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable and that other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control bacterial strains to control the technical aspects of the laboratory procedures. Standard eradomycin powder should provide the following MICs with these quality control strains:

Microorganisms	MIC Ranges ⁶⁸ (μg/mL):
Staphylococcus aureus ATCC 29213	0.016-0.12
Haemophilus influenzae ^c ATCC 49247	1.0-4.0
Streptococcus pneumoniae ^d ATCC 49619	0.002-0.016

^e This quality control range is applicable to only H. influenzae ATCC 49247 tested by a microdilution procedure using HTM.¹

Diffusion Techniques

Quantitative methods that require measurement of zone diameters of growth inhibition provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with eradomycin (equivalent to 15-mcg eradomycin) to test the susceptibility of bacteria to eradomycin. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for eradomycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a cradomycin disk (equivalent to 15-mcg eradomycin) should be interpreted according to the following criteria.

For testing non-fastidious aerobic bacteria:

Zone Diameter (mm)	Interpretation
≥23	Susceptible (S)
20-22	Intermediate (I)
≤19	Resistant (R)

For testing Haemophilus spp.e:

Zone Diameter (mm)	Interpretation ^f
--------------------	-----------------------------

^{68 290/44} NCCLS will also have impact

^d This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.¹

≥16	Susceptible (S)
13-15	Intermediate (I)
≤12	Resistant (R)

This zone diameter standard is applicable only to tests with Haemophilus spp. using HTM.²

For testing Streptococcus spp. including Streptococcus pneumoniae ^d:

Zone Diameter (mm)	Interpretation
≥20	Susceptible (S)
17-19	Intermediate (I)
≤16	Resistant (R)

These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for eradomycin.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See CLINICAL PHARMACOLOGY section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product)

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the eradomycin equivalent to a 15-mcg eradomycin disk should provide the following zone diameters in these laboratory quality control strains:

Zone Diameter Ranges

Staphylococcus aureus ATCC 25923 XXXXXmm Haemophilus influenzaeh ATCC 49247 XXXXXmm Streptococcus pneumoniaei ATCC 49619 XXXXXmm

Summaries of susceptibility interpretive criteria and acceptable quality control ranges for eradomyin to be used for validation of susceptibility test results can be shown in the following tables:

Susceptibility Interpretive Criteria for Eradomycin

	-				•	
Microorganisms	MIC (μg/mL)			Disk Diffusion (mm)		
	S	I	R	S	I	R
Aerobic Non-Fastidious	≤2	4	≥8	≥23	20-22	≤19
Haemophilus spp.	<u>≤</u> 4	8	≥16	≥16	13-15	<u>≤</u> 12
Streptococcus spp. including S.pneumoniae	≤0.5	1	≥2	≥20	17-19	<u><</u> 16

S = susceptible, I = intermediate, R = resistant

^h This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using HTM.²

¹ This quality control range is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.2

Acceptable Quality Control Ranges for Eradomycin To Be Used In Validation of Susceptibility Test Results

Quality Control Strain	MIC (mcg/mL)	Disk Diffusion (mm)
Streptococcus pneumoniae ATCC 49619	0.002-0.016	xxxxx
Haemophilus influenzae ATCC 49247	0.03-0.12	XXXXXX
Staphylococcus aureus ATCC 25913	0.016-0.12	Not Applicable
Staphylococcus aureus ATCC 25923	Not Applicable	xxxxx

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INDICATIONS AND USAGE

ERADOMYCIN Filmtab tablets are indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Adults:

Pharyngitis/Tonsillitis due to Streptococcus pyogenes (The usual drug of choice in the treatment and prevention of streptococcal infections and the prophylaxis of rheumatic fever is penicillin administered by either the intramuscular or the oral route. ERADOMYCIN is generally effective in the eradication of S. pyogenes from the nasopharynx; however, data establishing the efficacy of ERADOMYCIN in the subsequent prevention of rheumatic fever are not available at present.)

Acute maxillary sinusitis due to Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae

Acute bacterial exacerbation of chronic bronchitis due to Haemophilus influenzae, Moraxella catarrhalis, Haemophilus parainfluenzae or Streptococcus pneumoniae

Pucumonia due to Mycoplasma pneumoniae, Streptococcus pneumoniae, or Chlamydia pneumoniae (TWAR)

In patients who fail therapy, susceptibility testing should be done if possible. If resistance is demonstrated, alternative therapy is recommended. (For information on development of resistance see Microbiology section.)

CONTRAINDICATIONS

ERADOMYCIN is contraindicated for patients with a known hypersensitivity to ERADOMYCIN or any macrolide or ketolide antibiotics.

WARNINGS

ERADOMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING THIS DRUG, THE PATIENT SHOULD BE APPRISED OF $?^{69-70-71}$. (See PRECAUTIONS -Pregnancy.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ERADOMYCIN, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

69 Seg 1 70 Seg 2 71 Seg 3

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of "antibiotic-associated colitis".

Document 362-5

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against Clostridium difficile colitis.

PRECAUTIONS

General:

ERADOMYCIN is principally exercted via the liver. ERADOMYCIN may be administered without dosage adjustment to patients with hepatic impairment⁷² and normal renal function⁷³. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

Information to Patients: ERADOMYCIN tablets can be taken with or without food⁷⁴.

To be written pending outcome of drug interaction studies.

Planned drug interaction studies:

- 1) Ketoconazole¹
- 2) Impact of rifampin on 773^{76}
- 3) Impact of 773 on oral contraceptives⁷⁷
- 4) Impact of 773 on theophylline 75) Digoxin⁷⁹
- 6) Impact of 773 on midazolam⁸⁰
 7) Nifedipine⁸¹
- 8) Statin⁸²
- 9) Warfarin 83
- 10) Carbamezapine⁸⁴
- 11) Cyclosporin⁸
- 12) Loratadine⁸⁶

Potentially add general CYP3A statements rather than individually doing studies on individual drugs

Mutagenesis, Carcinogenesis, Impairment of Fertility:

⁷² M99-126	Hepatic study
⁷³ M00-FFF	Renal study
⁷⁴ M00-AAA	Final biostudy
⁷⁵ 100093	
⁷⁶ 100090	M00-156
⁷⁷ <u>100100</u>	M99-128
⁷⁸ 100101	M99-139
$\frac{79}{100102}$	
80_{100089}	M00-155; If does not increase midazolam conc (not likely), no
	need to do 100103 or 100104
⁸¹ 100003	Pending
82 <u>100104</u>	Pending
83 <u>100105</u>	
⁸⁴ 100107	
$\frac{85}{100108}$	
86 100109	

The following in vitro mutagenicity tests have been conducted with ERADOMYCIN:

In Vitro Cytogenetics Assay in Human Lymphocytes⁸⁷ Mouse Lymphoma Assay⁸⁸ Mouse Micronucleus Test⁸⁹ Bacterial Reverse-Mutation Test (Arnes Test)⁹⁰.

All tests had negative results.

Fertility and reproductive studies have shown that daily doses of up to ? mg/kg/day (X times the recommended maximum human dose based on mg/m^2) to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after ? mg/kg/day were X times the human serum levels. $^{91.92-93}$

In rabbits, no treatment-related effects on fetal viability or growth were observed. 91

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ERADOMYCIN.

Pregnancy: Category B or C95.

X number teratogenicity studies in rats (three with oral doses and one with intravenous doses up to X mg/kg/day administered during the period of major organogenesis) and two in rabbits at oral doses up to X mg/kg/day (approximately X times the recommended maximum human dose based on mg/m²) or intravenous doses of X mg/kg/day administered during gestation days X to X failed to demonstrate any teratogenicity from ERADOMYCIN. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of X mg/kg/day administered during gestation days X to X. Plasma levels after X mg/kg/day were X times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of X mg/kg/day (X and X times the recommended maximum human dose based on mg/m², respectively) during gestation days X to X. Cleft palate was also seen at X mg/kg/day. The X mg/kg/day exposure resulted in plasma levels X times the human serum levels. In monkeys, an oral dose X mg/kg/day (an approximate equidose of the recommended maximum human dose based on mg/m²) produced fetal growth retardation at plasma levels that were X times the human serum levels.

There are no adequate and well-controlled studies in pregnant women. ERADOMYCIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

Nursing Mothers%:

It is not known whether ERADOMYCIN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ERADOMYCIN is administered to a nursing woman. It is known that ERADOMYCIN is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk. Preweaned rats, exposed indirectly via consumption of milk from dams treated with 150 mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma.

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87 <u>100111</u>
88 100114
89 <u>100116</u>
90 100117
91 \overline{100018}
                        Seg 1
92
   100120
                         Seg 2 (rats)
    100119
                         Seg 3
   100106
   100119
                        Seg 3
96 <u>100110</u>
                        Study TBD
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Pediatric Use:

The safety and effectiveness of ERADOMYCIN in pediatric patients have not been established If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it...]

Geriatric Use 97:

In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 150 mg every 24 hours. the maximum serum concentrations and area under the curves of ERADOMYCIN were increased? compared to those achieved in healthy young adults. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. Dosage adjustment should be considered in elderly patients with severe renal impairment.

[If clinical studies did not include sufficient numbers (100) of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection of PRECAUTIONS shall include the following statement: "Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."]

ADVERSE REACTIONS

The majority of side effects observed in clinical trials were of a mild and transient nature.

The most frequently reported events in adults were diarrhea (X%), nausea (X%), abnormal taste (X%), dyspepsia (X%), abdominal pain/discomfort (X%), and headache $(X\%)^{98}$. Most of these events were described as mild or moderate in severity. Of the reported adverse events, only X% was described as severe.

In sinusitis studies conducted in adults comparing ERADOMYCIN to amoxicillin/clavulanic acid, there were fewer adverse events involving the digestive system in ERADOMYCIN-treated patients compared to amox/clavtreated patients (X% vs X%; p<0.01). Twenty percent of amoxicillin/clavulanic acid-treated patients discontinued therapy due to adverse events compared to 4% of ERADOMYCIN-treated patients.

Taste/GI comparable to Zithromax in AECB study?

Changes in Laboratory Values⁹⁹: Changes in laboratory values with possible clinical significance were as follows:

Hepatic - elevated SGPT (ALT) < X%; SGOT (AST) < X%; GGT < X%; alkaline phosphatase <X%; LDH < X%; total bilirubin < X%

Hematologic - decreased WBC < X%; elevated prothrombin time X%

Renal - elevated BUN X%; elevated serum creatinine < X%

GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

DOSAGE AND ADMINISTRATION

ERADOMYCIN[®] Filmtab[®] (ERADOMYCIN tablets may be given with or without food¹⁰⁰.

M01-AAA Study in elderly; need final dosage form/dose Phase III studies gg $^{100} \, \underline{_{100064}}$ M97-716

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	Dosage	Normal Duration
Infection	(q24h)	(days)
Pharyngitis/Tonsillitis	150 mg	5 days
Acute bacterial sinusitis	150 mg	10 days
Acute exacerbation of		
chronic bronchitis:	150 mg	5 days
Community-acquired pneumonia	_	-
including mycoplasma, chlamydia and		
legionella		
_	$150~\mathrm{mg}$	7-10 days

ERADOMYCIN may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function 101 102.

HOW SUPPLIED

ERADOMYCIN [®] Filmtab [®] (ERADOMYCIN tablets) are supplied as COLOR oval film-coated tablets containing 150 mg of ERADOMYCIN imprinted (on one side) in COLOR with the Abbott logo and a two-letter Abbo-Code designation, DK, in the following packaging sizes:

Bottles of 30 (NDC XXXX-XXX), ABBO-PAC unit dose strip packages of 100 (NDC XXXX-XXXX-XX), and RAD-PAK™ unit-of-use compliance package of 5 tablets in individual blisters.

CLINICAL STUDIES

Indication XXX

In a controlled clinical study of XXX performed in the United States, where significant rates of both penicillin-resistant and macrolide-resistant Strep, pneumoniae were observed, ERADOMYCIN was compared to XXX. In this study, very strict evaluability criteria were used to determine clinical response. For the XXX patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the post-therapy visit was XX% for ERADOMYCIN and XX% for the XXX.

In a smaller number of patients, microbiologic determinations were made at the pre-treatment visit. 'The following presumptive bacterial cradication/clinical cure outcomes (i.e., clinical success) were obtained:

 $^{101} \ \underline{100070}$

Hepatic study (M99-126)

 $\frac{-102}{100071}$

Renal study (TBD)

Error! Bookmark not defined.U.S. Acute XXX Study

ERADOMYCIN vs. Comparator XXX

EFFICACY RESULTS			
PATHOGEN	OUTCOME		
S. pneumoniae	ERADOMYCIN success rate, X/X (X%) control X/X (X%)		
H. influenzae*	ERADOMYCIN success rate, X/X (X%), control X/X (X%)		
M. catarrhalis	ERADOMYCIN success rate, X/X (X%), control X/X (X%)		
S. pyogenes	ERADOMYCIN success rate, X/X (X%), control X/X (X%)		
Overall	ERADOMYCIN success rate X/X (X%), control X/X (X%)		

None of the Strep. pneumoniae isolated pre-treatment was resistant to ERADOMYCIN; X% were resistant to the control agent.

Safety:

The incidence of adverse events in all patients treated, primarily diarrhea and vomiting, did not differ clinically or statistically for the two agents.

In two other controlled clinical trials of indication XXX performed in the United States, where significant rates of penicillin-resistant and macrolide-resistant Strep, pneumoniae were found, ERADOMYCIN was compared to XXX. In these studies, very strict evaluability criteria were used to determine the clinical responses. In the XXX patients who were evaluated for clinical efficacy, the combined clinical success rate (i.e., cure and improvement) at the post-therapy visit was XX% for both ERADOMYCIN and the control.

For the patients who had microbiologic determinations at the pre-treatment visit, the following presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) were obtained:

Error! Bookmark not defined. Two U.S. Acute XXX Studies ERADOMYCIN vs.

Comparator XXX

EFFICACY RESULTS

OUTCOME
ERADOMYCIN success rate, X/X (X%), control X/X
(X%)
ERADOMYCIN success rate, X/X (X%), control X/X
(X%)
ERADOMYCIN success rate, X/X (X%), control X/X
(X%)
ERADOMYCIN success rate, X/X (X%), control X/X
(X%)
ERADOMYCIN success rate, X/X (X%), control X/X
(X%)

Of the Strep. pneumoniae isolated pre-treatment, X% were resistant to ERADOMYCIN and X% were resistant to the control agent.

The incidence of adverse events in all patients treated, primarily diarrhea (X% vs. X%) and XXX (X vs. X%)

was clinically and statistically lower in the ERADOMYCIN arm versus the control arm.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

ERADOMYCIN is rapidly and well-absorbed with dose-linear kinetics, low protein binding, and a high volume of distribution. Plasma half-life ranged from 1 to 6 hours and was species dependent. High tissue concentrations were achieved, but negligible accumulation was observed. Fecal clearance predominated. Hepatotoxicity occurred in all species tested (i.e., in rats and monkeys at doses 2 times greater than and in dogs at doses comparable to the maximum human daily dose, based on mg/m²). Renal tubular degeneration (calculated on a mg/m² basis) occurred in rats at doses 2 times, in monkeys at doses 8 times, and in dogs at doses 12 times greater than the maximum human daily dose. Testicular atrophy (on a mg/m² basis) occurred in rats at doses 7 times, in dogs at doses 3 times, and in monkeys at doses 8 times greater than the maximum human daily dose. Corneal opacity (on a mg/m² basis) occurred in dogs at doses 12 times and in monkeys at doses 8 times greater than the maximum human daily dose. Lymphoid depletion (on a mg/m² basis) occurred in dogs at doses 3 times greater than and in monkeys at doses 2 times greater than the maximum human daily dose. These adverse events were absent during clinical trials.

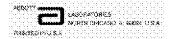
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1.

2.

Filmtab - Film-sealed tablets, Abbott TM - Trademark

Revised: January, 1997



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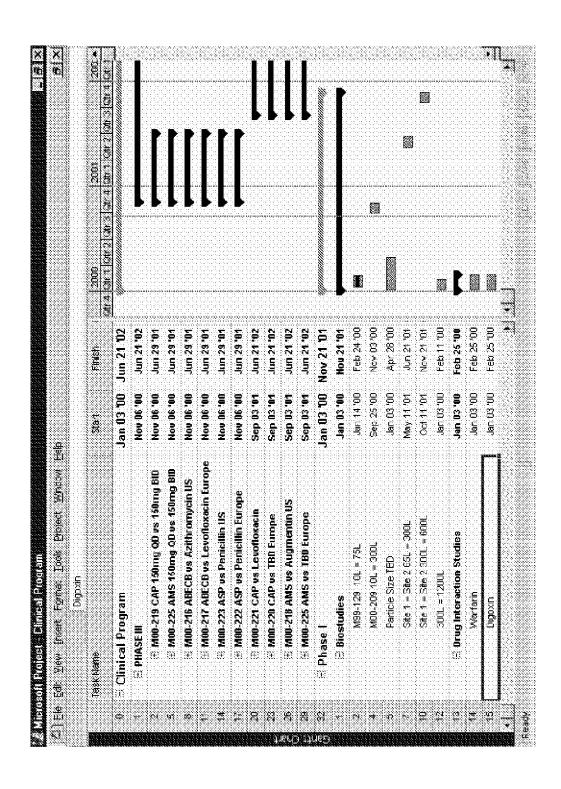
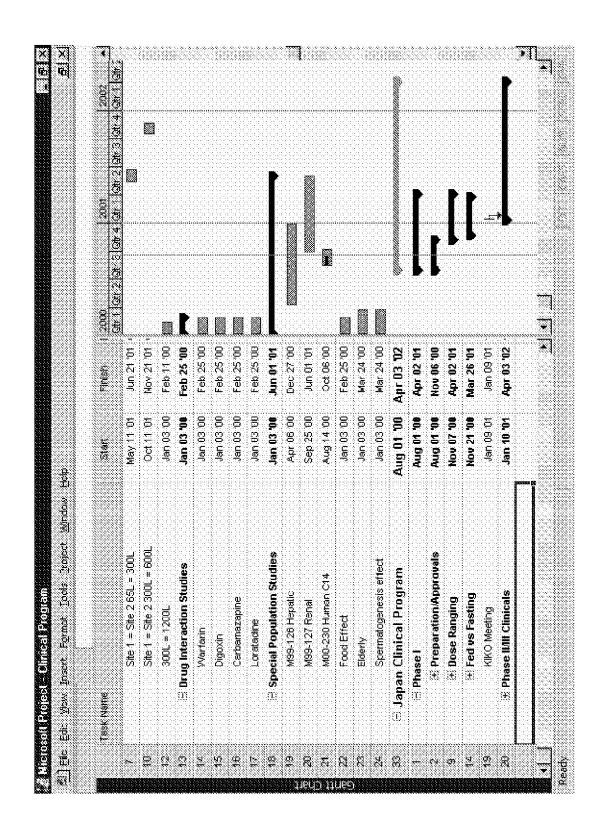
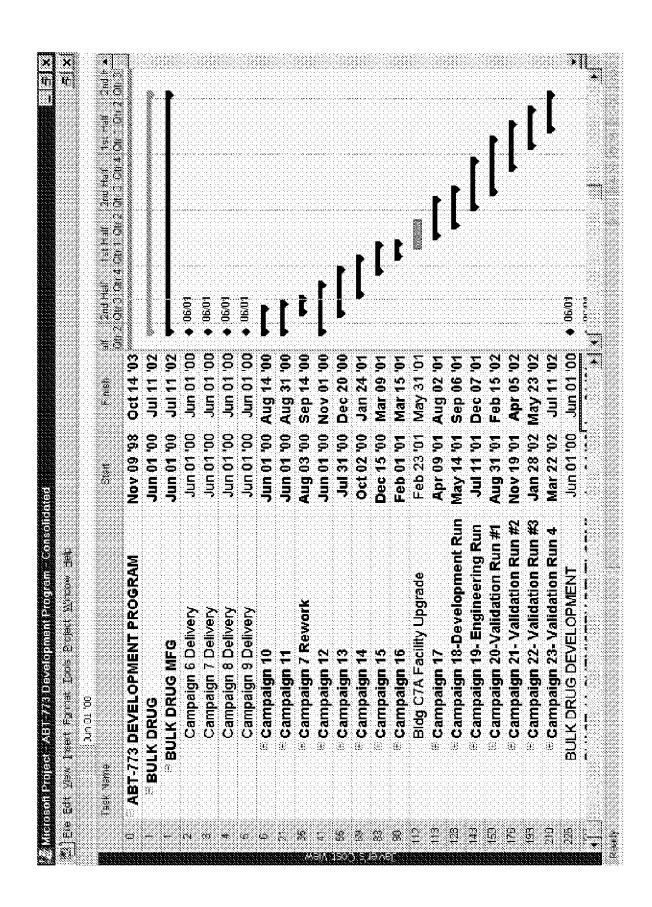
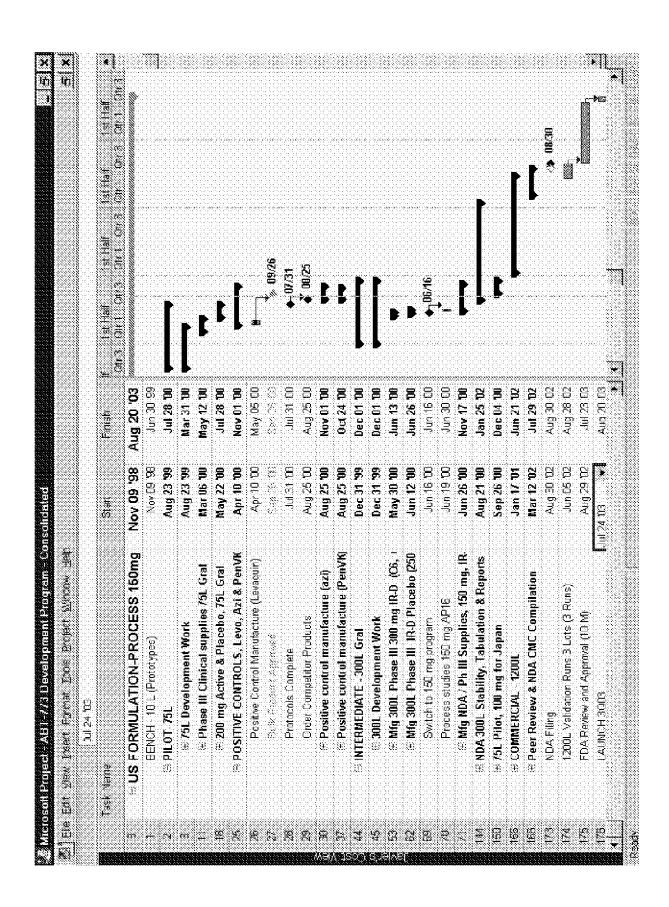


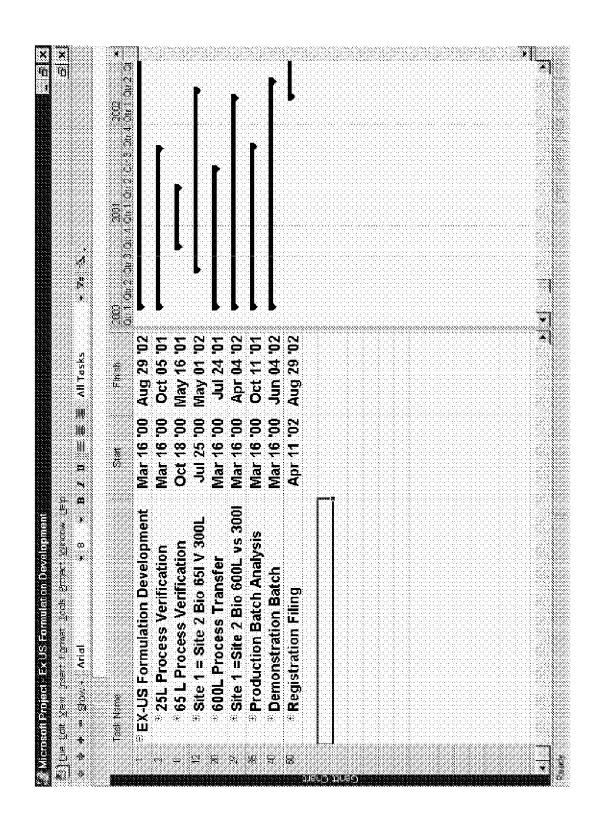
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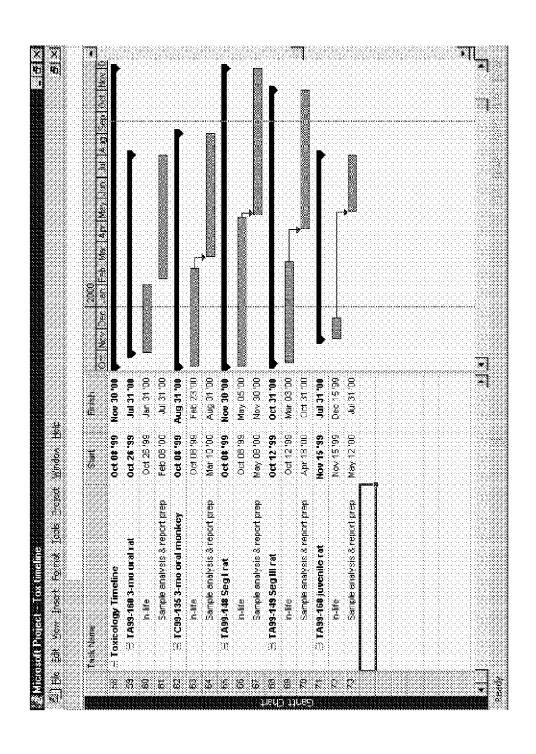
Document 362-6







Document 362-6



Filed 03/10/2008

5.0 Project History

- 5.1 Expert Strategic Review Process Summaries
- 5.2 Highlights re: NCE
- ABT-773 was approved by PPCC in 03/97 for development by the Macrolide Venture. Projected NDA date was 12/00.
- Fifty kg of drug was delivered in 1997. Drug chemistry and cost of drug was a major challenge to development cost and timing. NDA projected date was moved to 03/01 with 50% probability.
- First Phase I study was initiated in Netherlands in 11/97. Based on PK results, the request for a QD ER formulation and no major breakthroughs in chemistry, the NDA projected date was moved to 06/02 with 80% probability.
- All process chemistry efforts and delivery activities were put on hold in 04/98 due to concerns of GI/taste issues with the drug. A comparative safety study using 300mg and 600mg/day of ABT-773 vs Clari 500mg bid was initiated. NDA projected date was moved to 09/02 with 80% probability.
- The encouraging safety results lifted the hold on the process chemistry and delivery activities. For 5 months there were no efforts on process research and delivery activities for drug substance. The first ER prototypes were not acceptable. A Phase IIA study using unformulated capsules was initiated in Europe in AECB patients by end of 1998, NDA projected date was kept at 09/02 with 80% probability.
- Significant breakthroughs were achieved in bulk drug synthesis and an ambitious development program was initiated by end of 1998 to develop a QD formulation. Three immediate release and twelve extended release formulations were evaluated with immediate release capsule formulation (IR-A) serving as the reference formulation. After a review of the preliminary data of these studies, an immediate release tablet formulation (IR-C) was chosen on 8/99 for further development based on pharmacokinetics, safety, and ease of manufacture.. The Venture had undertaken a challenging chemistry, formulation and clinical development plan and the NDA projected date had been brought forward to 12/01.
- The Phase 2a study indicated that 100 mg TID is an effective dose in ABECB in terms of clinical and bacteriological outcomes and has an acceptable safety profile. Based on these results, 300 mg QD was selected as the middle dose for the Phase 2b trials (a preferred regimen over a TID regimen for patience compliance) since the 100 mg TID had demonstrated acceptable efficacy/safety and the QD regimen provided greater exposure than the TID regimen.
- Three Phase 2b studies were started in Sept. 1999 in both the US and EU investigating ABT-773 once daily doses. M99-054 - Community-acquired pneumonia (300 mg or 600 mg once daily for 7 days). M99-053 - Acute bacterial sinusitis (150 mg, 300 mg, or 600 mg once daily for 10 days). M99-048 -Acute bacterial exacerbation of chronic bronchitis (150 mg, 300 mg, or 600 mg once daily for 5 days)
- Scale-up activities to develop a 300mg tablet were initiated at the 751, pilot scale in 9/99, moving to a 300L intermediate scale in Jan 2000. A bioequivalence study was successful comparing the bench scale clinical lots to the 75L pilot scale lots.

- The efficacy (clinical/bacteriology) data from the Phase 2b studies indicated that 150 mg, 300 mg and
 600 mg were effective in treating subjects with ABECB (5 days) and ABS (10 days). The 300 mg and
 600 mg were both effective doses to treat CAP (7 days) subjects.
- The safety data indicated that all doses studied did not yield any clinically significant safety
 abnormalities as far as elevation of liver enzymes or QT prolongation are concerned. The 300 mg and
 600 mg doses exhibited moderate amounts of taste disturbance and GI side effects, which were mainly
 diarrhea, nausea and vomiting
- Based on the Phase 2b efficacy and safety results, the decision was made to change the tablet dose from 300mg to 150mg. This decision moved the regulatory filing date forward 8 months to Aug 2002 and postponed the start date of the Phase III clinical studies to Nov 2000, in order to prepare 150mg clinical supplies.
- A Japanese bridging study was conducted in Hawaii to evaluate safety and pharmacokinetics of Japanese and non-Japanese subjects. Over the studied doses (150, 300 and 600 mg single and multiple QD), ABT-773 AUC but not Cmax deviated from dose-proportionality in the Japanese and non-Japanese subjects. At equivalent doses, the Japanese subjects had about 50% greater ABT-773 AUC than the non-Japanese subjects. Based on this result, the Japanese Phase I program will be repeated in Japan. Once Phase I results are available and the clinical agency KIKO has been consulted, the Phase II/III program in Japan will be finalized. It is unknown at this time if a separate Japanese dose will be required.

5.1 Historical Changes to ABT-XXX Target Product Profile

Table 4.0.a Historical Changes to ABT-XXX Target Product Profile						
PPCC/DDC Profile (12/10/97)	Current Profile (9/00)	Rationale for Profile Change				
Activity against Gram +, Gram -, atypicals	Activity against Gram +. Gram atypicals	No Change				
Activity against <i>H. influenzae</i> = azi	Activity against <i>H. influenzae</i> = azi	No Change				
Active against 80% of Gram + resistant strains of efflux and MLS-c	Active against 80% of Gram + resistant strains of efflux and MLS-c	No Change				
Active against most macrolide resistant pathogens on a bacterial-worldwide-susceptibility panel	Active against most macrolide resistant pathogens on a bacterial-worldwide-susceptibility panel	No Change				
Maintain balanced plasma/tissue levels similar to clari	Maintain balanced plasma/tissue levels similar to clari	No Change				
Incidence of GI side effects=cephalosporins	Incidence of GI side effects=azi	Azithromycin is a more important competitor in the U.S.				
Incidence of drug-interactions = clari, no contraindications	Incidence of drug-interactions = clari, no contraindications	No Change				
QD dosing adult/tablet	QD dosing adult/tablet	No Change				
QD dosing ped OS	QD dosing ped OS	No Change				
BID dosing for IV	QD dosing for IV	Current competition is QD				
Less painful IV at injection site than clarii	Comparable pain at injection site than azi	Azi has less pain than clari.				
Less metallic taste for tablet than clari.	Less metallic taste than clari XL	Clari XL now available.				

OS equal in taste to cephalosporins	OS equal in taste to Azi. Omnicef	Azi and Omnicef most important comparators.
5-day therapy for most indications; up to 10 days for serious infections, 3 day therapy for pharyngitis.	5-day therapy for most indications	No Change
Bulk drug cost less than \$2500/kg at launch and \$1250/kg 3 years post launch.	COGS > 80% SMM at launch	No Change
Maximum adult does per day of 1 gram.		No Change
Can be given with or without food.		Food effect study to be repeated with final formulation, current studies indicate better absorption with food.

ABT-773 Update February 12, 2001

Introduction

ABT-773 is a ketolide antimicrobial, an evolutionary step from the macrolide antimicrobials such as erythromycin and the new generation macrolides like clarithromycin and azithromycin. It is in phase III development as a replacement to clarithromycin.

The antibiotic market is a large market (\$20.5 Billion in 1999) and is expected to expand on a global sales basis (\$26.5 Billion in 2005). The majority of the markets sales are in the oral tablet/capsule segment. Market sales increases are being driven by replacement of older/cheaper agents with branded agents. Zithromax has driven market demand for cost/convenience/tolerability, while the quinolones (Levaquin, Tequin, Avelox) are the fastest growing segment, playing into resistance concerns. Resistance is a major driving force for both the quinolones and ketolides development.

Ketolides are a Novel Class of Antimicrobial

- Active includes key respiratory tract infection pathogens including macrolide and penicillin resistant S. pneumoniae and S. pyogenes
- Bactericidal activity
- · Prolonged post antibiotic effect
- · Reduced resistance development

ABT-773 is the most active ketolide presently under development. It is 5 to 10 times more active than teilthromycin (Aventis ketolide) against *S. pneumoniae* and *S. pyogenes* including resistant strains. It has equal activity to telithromycin and azithromycin against *H. influenzae*. The increased activity can be attributed increased ribosomal binding. Compared to macrolides that bind only to domain V, ABT-773 binds to both domains II and V. The binding is essentially irreversible and provides bactericidal activity against *S. pneumoniae*.

Key issues facing the ABT-773 development program are summarized below

QTc Issues

The potential for QTc prolongation is currently a prominent issue facing drug development across therapeutic areas-worldwide. Antimicrobial agents including macrolides and quinolones are of concern to regulatory agencies. There is considerable scientific uncertainty in relating the findings from in vitro assays and animal models to clinical risk of malignant arrhythmias. In an effort to gain more

knowledge these agencies are requiring the pharmaceutical companies to do additional test including

- ICH guidelines require data from animal models and 200 patients
- FDA is in the process of evaluating all drug class known to have a potential for prolonging QTc (erythromycin and clarithromycin)
- FDA has question whether ketolides behave like macrolides
- FDA requested additional dog tox work to evaluate QTc of ABT-773
- ABT-773 studies required including ECG monitoring in pivotal Phase 3 studies.
- FDA may require a Phase I study in patients with underlying cardiac disease, but the design for these studies has not been determined.
- Some antimicrobials now contain warnings for QT prolongation such as moxifloxacin.
- Telithromycin (Ketek) data residing at FDA will be reviewed by FDA Advisory Committee at a meeting scheduled for May 2001 probably related to concerns about efficacy and not related to QTc concerns.

The ketolide ABT-773 will be considered guilty until proven innocent because it is related to erythromycin and clarithromycin which are also suspect and under scrutiny. ABT-773 has the following data related to its potential or lack of potential to affect the QT interval.

- Preclinical data positive for QTc dose response.
- A possible dose effect in Phase I at total daily dose ≥800 mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole. (Increased ABT-773 Cmax 5X)
- No concentration response in Phase I studies (≤300mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies. (150 mg QD to 600 mg QD)

The Venture plan for dealing with the uncertainties related to developing a drug which has an unknown potential for prolonging the QT intervals is to pro-actively attempt to find out as much about our drug and the science related to QTc by;

- Completed preclinical evaluation of ABT-773
- Initiate FDA recommended dog studies.
- Completed ECG monitoring of >200 patients in Phase II and III
- Continue to monitor QTc and electrolytes in Phase III programs.
- Perform FDA requested study of QTc in patients with pre-existing cardiac disease; perform phase I study as required by CPMP.
- IV ABT-773 Phase I study will monitor QTc carefully
- Consult with Drs. Morganroth and Moss QTc advisors.

Liver Toxicity Issues

The FDA has similar concerns regarding the potential for liver toxicity of new drugs as it has for QTc issues, since both of these problems have resulted in

drugs being removed from the market shortly after approval. The concerns have been directed at the quinolones, but all antimicrobials are under going extensive evaluations. The FDA has a meeting on guidance to industry on how to study the potential for liver toxicity, scheduled for February 11-12, 2001. Jean Fox will attend this meeting and report back on it so that we will be able to update this topic at the February meeting.

In the Japanese bridging study run in Hawaii we saw increases in LFTs in Japanese subjects. This was very disturbing, since increases in LFTs were seen only in the Japanese subjects. In addition the Japanese subjects had AUCs which were 50% higher than the western subjects. LFTs in over 1000 western subjects did not show any problems. Since, the Japanese subjects with elevated LFTs did not show a dose response, it was felt that the changes in LFTs might be related to the high caloric diet on the unit. To answer this question Phase I food interaction and a repeat of the bridging study was preformed in Japan. The results of this study showed no evidence of any problem with LFTs in the Japanese or Caucasians. Based on the encouraging results we will continue moving forward with the Japan Program.

Phase III Tablet Program

The Phase III tablet program is underway after several delays related to manufacturing of the 150 mg tablet to replace the 300 mg tablets and the late date (11/27/00) of the FDA End of Phase II meeting. The present plan is to complete the Phase III 150 mg once daily indications in the US and Europe this year. These studies include two pharyngitis studies compared to penicillin 500 mg TID, one ABECB study in the US compared to Azithromycin, and one European ABECB study compared to Levofloxacin. The CAP and sinusitis dose selections studies are running globally, but no European sites are enrolling yet due to the changes in the protocol following the FDA End of Phase II meeting. We are increasing sites and planning to go to the Southern Hemisphere if needed to complete the studies before the start of the fall respiratory season. These changes have added additional costs that will add approximately \$5.0 MM to the budget.

The results of the CAP and Sinusitis studies have the potential of generating divergent development paths based on differences in AI and PPD regulatory and commercial considerations. PPD would prefer to have 150 mg once daily for all indications and AI would prefer 150 mg once daily for pharyngitis and ABECB and 150 mg BID for CAP and sinusitis. Once we complete the study we will need to meet to iron out the possible options.

ABT-773 IV Formulation Program

Filed 03/10/2008

The IV formulation program is presently unfunded. The IV program is important to overall program because of the following;

- · Hospital formulary acceptance
- XX% share gain in Tab sales due to step-down therapy
- · Positions 773 for serious infections
- Support for S. pneumoniae resistance claim
 - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
- Provide additional information on QTc effects

The ABT-773 IV program received partial funding last year both from PPD and HPD, but has not been funded for 2001. The following outlines the IV program fund and funding needed.

- PPD/HPD Collaboration initiated 9/99
- PPD funded Program 01/00-08/00 (\$1.4MM)
 - Formulation development (lactate salt, lyophilized powder)
 - Animal pain models
 - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 (\$0.8MM)
 - Two week Tox study (rat)
 - Clinical supplies for Phase I
 - Stability program
- 2001 funding
 - HPD first pass funding cut for 773 IV (\$7MM)
 - Milestone funding to Phase I Go/No Go (\$1MM)
- Total program development costs 2000 2003 (\$22.5MM)

The clinical program with 2001 funding decision in February will included;

•	Single Dose-rising Phase I study	Apr/01
•	Multiple Dose Phase I with selected dose	June/01
٠	File US IND	Oct/01
٠	Initiate Phase III	Dec/01
	 2 step-down CAP studies (US/Europe) 	

- 2-3 days dosing
- Two seasons to complete

 Filing Aug/03

The Venture would recommend funding the Phase I study to determine safety and tolerability profile as a GO/No Go decision. Assuming a GO decision we would need \$7 MM 2001 to start Phase III program.

Pediatric Program

Filed 03/10/2008

The pediatric suspension program is on hold. ABT-773 is 5 to 7 times more bitter than clarithromycin. This will make the development of an acceptable formulation very difficult. The first prototype tested had a taste that was better than clarithromycin but not as good azithromycin. The pharmacokinetics showed AUCs that were only 70% of the tablet formulation. Even with the difficulties of making an acceptable formulation the pediatric formulation would have benefits including increasing the perception of safety, better pricing and acceptance in European markets, and FDA requires studies in pediatrics. The Venture would recommend continuing the hold until we resolve other issues and then reevaluate possible ways of overcoming the taste problem.

Japan Development Program

The Japan development program is planned in coordination with Taisho and Dainabot. Taisho funds 10.69% of global development costs and 50% of local Japan costs. The Venture is attempting to use a bridging strategy is the primary plan for development in Japan. The Phase I studies in Japan which were initiated in response to the LFT problems in the first bridging study, have been completed. There were not increases in the LFTs of the Japanese or Caucasians in the study. We will be meeting with Taisho and Dainabot to formulate a plan to present to Kiko in the 2nd or 3rd Quarter.





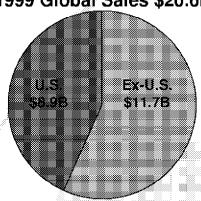
Agenda

- Introduction
- The molecule
- Phase III tablet program Issues
 - QT
 - Liver Function
 - Dosing
- IV program
- Pediatric program
- Japan program

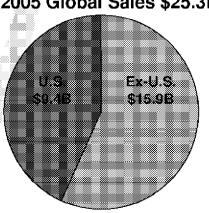


Global Antibiotic Market Sales Current vs Future Projection





2005 Global Sales \$25.3B



The antibiotic market is a large market and is expected to expand on a global sales basis



Antibiotic Resistance

Increasing sensitivity toward "appropriate use" may have negative impact on usage 🎩 Requires new agents to keep ahead of resistant pathogens; substitution of older generic agents with newer branded agents 1

Patent Expirations

May increase price sensitivity and bargaining power of MCOs 👢 Use of generic agents tend to decrease over time; obsolescence/resistance may further that trend a

Market expansion ex-US ☆

- Unmet Need 4
 - -Overall unmet need relatively low
 - -Cost, convenience, tolerability take on added importance
 - -Increasing use of "implied efficacy" metrics i.e. MICs, resistance surveillance, AUC/MIC, MPC, kill kinetics

Competition ■

- -6 NDAs/approvals in last 12 months; Avelox, Tequin, Factive, Spectracef, Ketek, Zyvox
- -Continued discovery/development activity by key competitors
- -High level of promotional activity

Negative driver -

Positive driver 1

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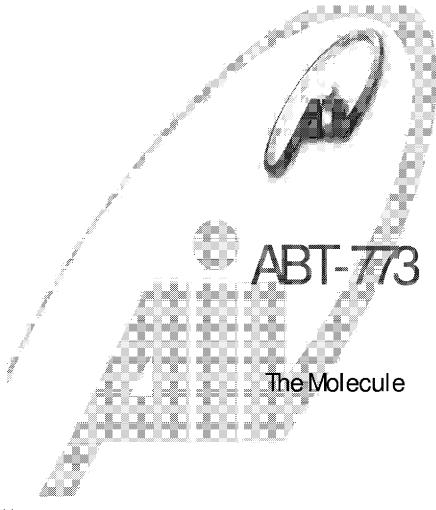
Key Success Factors U.S. vs ex-U.S.

	11000000	dec				
						U.S. Assessment Ex-U.S. Assessment
8	***	888			***	Réquires a certain baseline level offetticacy aeross all 🐃 💮 While also difficialt to différentière based on efficacy, efficacy.
				Efficacy	**	Indications as a "ticket to entry", but is difficult to differentiate agents based on efficacy approval, especially in CAP.
	***		- 1			Success of Zithromax and Levaguin have redefined Although important, markets are willing to bear somewhat
				Telerability	+++	expectations for tolerability of new agents, agents must offer very good folerability given numerous afternatives higher incidence of adverse events, provided they are not severe (i.e. taste perversion); over time, however, AE nurdles
	***	333		- 100 - 100 - 10		will continue to be increased Zithromax and recent quinclones have moved the market While in some cases durations are even shorter (azi 3 day
	Pi	ofile		Convenience	+**	toward short course therapies dosed once daily, Blaxin in ++ AECD), market levies relatively minor penalties for BID
				Resistance Claim	++	
		***		Price		Able lasset price in accordance with optimal acce/densand relationship, only moderate price sensitivity in market, though this could increase with increased number of generic relative to other apents.
						competitors over mid-terms Will take into consideration PK profile in addition to climical data, which could weaken argument for approval, given the
	Kegi	ilatoi	¥	Approvability	*	major area of cencern regulation risk is traggined; will require very strong clinical
+	3888	9888 9666		1000 1000 100		data if 150 mg QD is to be supported
	Profit	tabili	ty	coes		Due to pricing constraints, CGS represents a larger issue: Current estimation are 75% SMM attaurish rising to 82% peak
			4	Price	1	Assumes price parity to Zifhromax ++++ Profile may limit optimal pricing

+ Minor Factor

++ Moderate Factor

+++ Major Factor





ABT-773 Ketolide

•Quinolylallyl propenyl moiety at the 6-0 -position

- •Keto group at the 3-position
- •Carbamate group at the 11, 12-position

ABT-773



ABT-773 Ketolide

Ketolides are a Novel Class of Antimicrobial

- Active includes key respiratory tract infection pathogens including macrolide and penicillin resistant S. pneumoniae and S. pyogenes
- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development

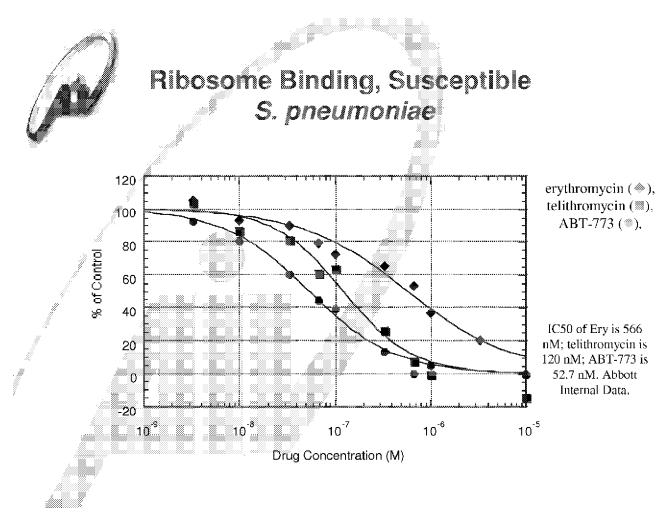


Microbiology

 $MIC_{90} \mu g/mI$

Organism	ABT-773	Ketek	Clari	Azi
S. pheumoniae ery-S	0.008	0.004	0.03	0.12
S. pneumoniae méi	0.12	1 .0	4.0	16.0
S. pnuemoniae erm	0.01	0.12	>32	>32
S. pyogenes ery-S	0.12	2.0	1.0	2.0
S. pyogenes ery-R	0.5	>8.0	>32	>32
M. catarrhalis	0.25	0.25	0.5	0.25
H. Influenzae	2.0	2.0	16	2.0
Legionella 👚 💮	2.0	2.0	0.06	1.0
M. Pneumoniae	<0.005	< 0.005	0.008	<0.005
C. Pneumoniae	0.015	0.06	0.06	0.12







ABT-773 Displacement in Susceptible *S. pneumoniae* 2486

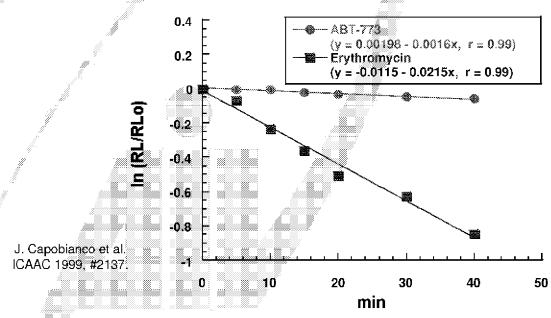
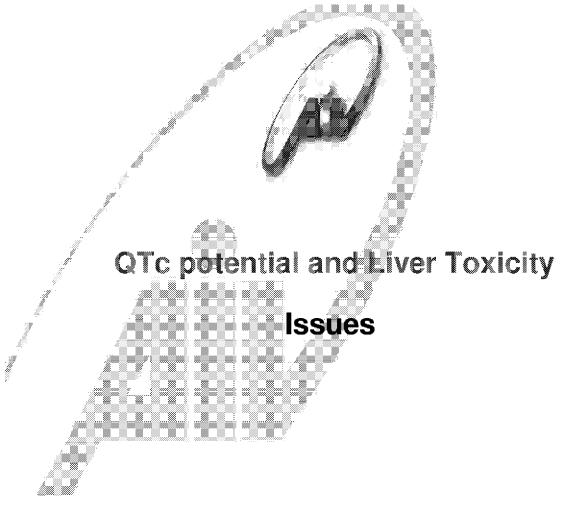
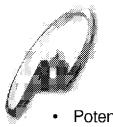


EXHIBIT 608 Part 5





QTc Prolongation Issues

- Potential for QTc Prolongation is a hot button worldwide
 - Antimicrobial agents including macrolides and quinolones are of concern to regulatory agencies
 - -/ CPMP guidelines require data from animal models and 200 subjects
 - FDA is in the process of evaluating all drug class known to have a potential for prolonging QTc (erythromycin and clarithromycin)
 - FDA has question whether ketolides behave like macrolides
 - FDA requested additional dog tox work to evaluate QTc
 - Required to include ECG monitoring in pivotal Phase 3 studies
 - FDA may require a Phase I study in patients with underlying cardiac disease
 - Some antimicrobials now contain warnings for QT prolongation
 - Telithromycin (Ketek) data residing at FDA
 - Advisory Meeting rescheduled to May 2001 probably not related to QTc concerns



QT_c Prolongation Issues

- Pre-clinical data positive for QTc dose response.
- A possible dose effect in Phase I at total daily dose >800 mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole.(Increased ABT-773 Cmax 5X)
- No concentration response in Phase I studies (≤300mg).
- · No consistent QT effect observed at clinical doses studied in Phase IIB studies. (150 mg QD to 600 mg QD)

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QT_c Prolongation Issues ABT-773 Plan

- Completed pre-clinical evaluation of ABT-773
- Completed ECG monitoring of >200 patients in Phase II and III
- Continue to monitor QTc and electrolytes in Phase III programs.
- Planning FDA requested study of QTc in patients with preexisting cardiac disease.
- IV ABT-773 Phase I study will monitor QTc carefully
- · Consult with Drs. Morganroth and Moss QTc advisors.



Liver Toxicity Issues

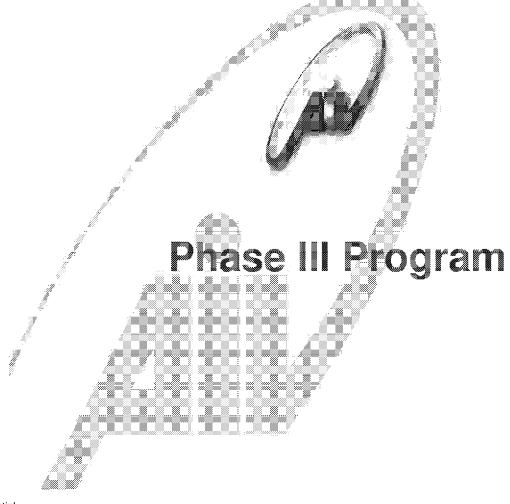
- Potential for liver toxicity is a concern for the FDA
 - Recent liver toxicity seen with Trovofloxacin are of concern to regulatory agencies.
 - Gemifloxacin recently not approved by FDA because of liver toxicity concerns.
 - FDA meeting on guides to industry on how to study liver function scheduled for February 11-12, 2001



Liver Toxicity Issues for ABT-773

- Preclinical tox showed some effect on the liver function.
- Japanese in bridging study showed increased LFTs.
- No evidence of LFT issue in Western subjects.
- No evidence of dose response.
- Repeat of Japanese bridging study in Japan showed No evidence of LFT increases in Japanese or Caucasians.
- ABT-773 plan for accessing problem
 - Continue to monitor LFT in Phase III programs.
 - Jean Fox will attend FDA meeting.

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Phase III Program Proposed Indications and Treatment Duration

Infection	Dosage	Duration
Pharyngitis/Tonsillitis due to:		
S. pyogenes*	150 mg QD	5 d
Acute bacterial sinusitis due to:		
H. influenzae	150 mg QD or BID	10 d
M. catarrhalis	150 mg QD or BID	10 d
S. pneumoniae**	150 mg QD or BID	10 d
Acute bacterial exacerbation of chronic		
bronchitis due to:	- 2000 (100 E) 	
H. influenzae	150 mg	5 d
tt parainfluenzae	150 mg	5 d
M. catarrhalis	150 mg	5 d
S. pneumoniae***	150 mg	5 d
Community-acquired		
pneumonia due to:		
C pneumoniae	150 mg QD or BID	10 d
H. influenzae	150 mg QD or BID	10 d
Ł. pneumophila	150 mg QD or BID	10 d
M. pneumoniae	150 mg QD or BID	10 d
S. pneumoniae**	150 mg QD or BID	10 d

Including macrolide-resistant strains.
Including penicillin-resistant and macrolide-resistant strains.



Phase III Program Studies Started in Year 2000

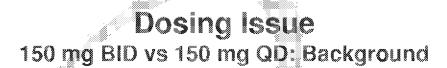
				100000000000000000000000000000000000000	
Study	Indication	ABT-773 Regimen	Comparator	Number Subjects	Location
M00-223	Pharyngitis	150 mg QD 5 days	Penicillin V	185/520	US (IND)
M00-222	Pharyngitis	150 mg QD 5 days	Penicillin V	©/520	EU (Non-IND)
M00-216	ABECB	150 mg QD 5 days	Azithromycin	131/600	US, Canada IND
M00-217	ABECB	150 mg QD 5 days	Levofloxacin	©/500	EU (Non-IND)



Phase III Program Studies Started in Year 2000, Con't

Dose Finding Studies for Sinusitis/CAP:

Study	Indication	ABT-773 Regimen	Comparator	Number Subjects	Location
M00-225	Sinusitis	150 mg QD <i>vs.</i> 150 mg BID 10 days	None	137/500	US, EU (IND)
M00-219	CAP	150 mg QD <i>vs.</i> 150 mg BID 10 days	None	76/500	US, Canada, EU (IND)



- Phase II data indicated 300 mg QD was not viable due to high levels of diarrhea (10-20%) and taste perversion (10-20%)
- Phase II ABECB and pharyngitis/tonsillitis data supported 150 mg QD
 - 150 mg QD currently being evaluated in ongoing phase III trials in these indications
- Dosing selection for CAP and sinusitis confounded by limited data
 - few bacterial isolates, particularly with H. flu in sinusitis
 - no 150 mg arm in CAP trial
- To increase probability of correct dose selection in CAP/sinusitis, the decision was made to undertake additional studies to generate more data in these indications
 - 150 mg QD vs 150 mg BID CAP & sinusitis trials ongoing
 - Decision facilitated by Decision Support Group, with joint Al & PPD consensus on decision

ABBT205069 Confidential



Dosing Issue

150 mg BID vs 150 mg QD: Implications of Decision

· For U.S. market:

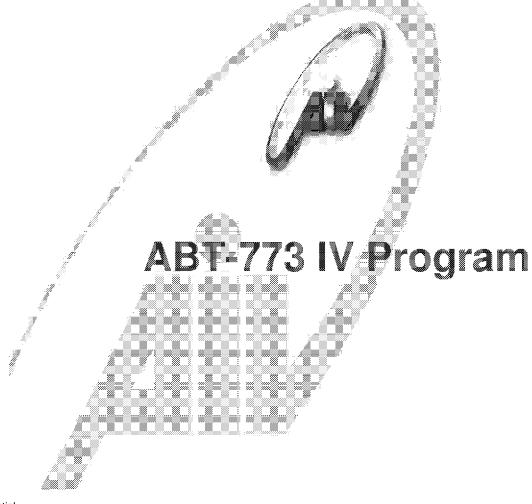
- Absence of consistent QD dosing for all indications represents a significant commercial hurdle
- Approval on indication-by-indication basis
- Optimal strategy for U.S. may be to pursue QD dosing for CAP/sinusitis

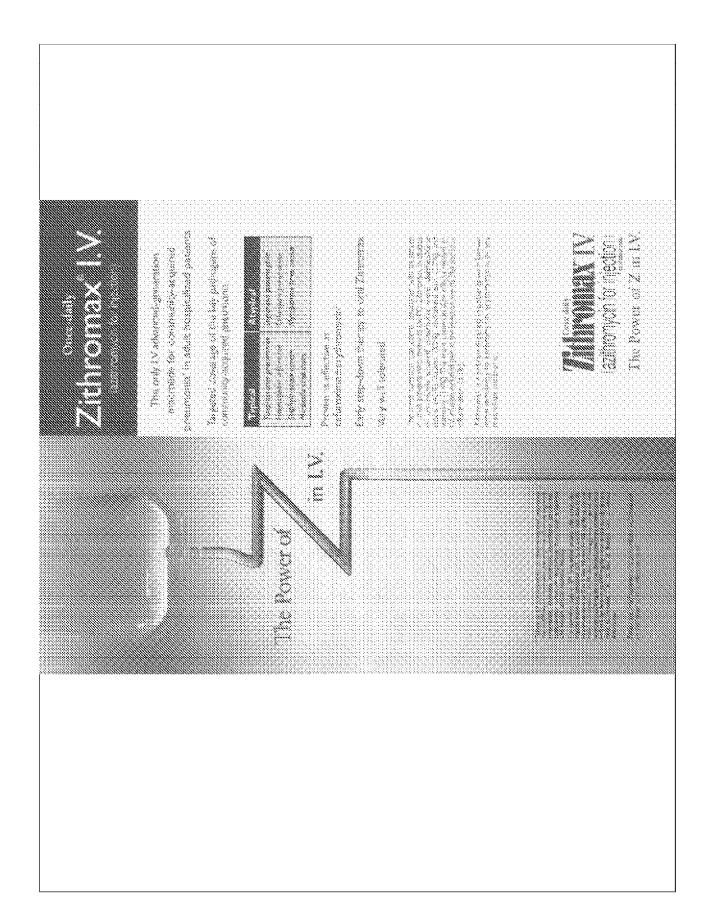
For ex-U.S. market;

- CAP data represents the "lynchpin" for approvability of the entire molecule, hence a conservative BID approach may result in lower regulatory/commercial risk
- Relatively minor commercial impact of BID dosing
- Optimal strategy for ex-U.S. may be to pursue BID dosing for CAP and perhaps sinusitis

A decision of 150 mg QD vs 150 mg BID in CAP & sinusitis will be made based on phase III data 2Q01

- Key ex-U.S. criteria for CAP approval include: a) satisfactory efficacy/eradication in severe CAP b) sufficient resistant isolates with satisfactory eradication c) treatment of bacteremic cases
- data may not show a clear "winner" due to relatively low power of studies; may be a
 difficult decision
- due to soft global flu season and protocol amendments, enrollment is behind plan and could impact timing of decision
- A plan to have divergent clinical programs in CAP/sinusitis may be an option





ABT-773 IV Formulation Strategic, Commercial, and Technical Value

- Strategic Value
 - IV represents a channel not currently served by Anti-infective Franchise
 - Leverages presence of Medical Center Reps and experience with ID community
- Commercial Value
 - IV availability figures favorably into decisions regarding formulary access to molecule
 - · potential advantage over telithromycin, which will not have an IV
 - · required to compete effectively with Zithromax, Tequir, Avelox which have IVs
 - Positive impact on tablet formulation
 - · estimated \$36MM incremental to peak tablet sales due to step-down therapy
 - Enhances overall "potency" image of brand
- Technical Value
 - Support for S. pneumoniae Resistance claim
 - FDA indicated that bacteremic patients will be important to establish body of evidence for this
 claim
 - Provides additional information on QT effects

IV launch currently lags tablet launch by 1 year; any further delays will reduce the potential value



ABT-773 IV Program Formulation Objectives

- Reconstituted solution. Once a day dosing. Low pain on injection
- Lyophilized powder, consisting of ABT-773 and a counter ion base.
- One strength, in a flip-top vial and the ADD Vantage system at launch.
- Diluent volume 100ML, with length of infusion (30 to 60 minutes) and type of diluent (Dextrose 5% and/or normal saline) TBD based on animal pain models, clinical and stability studies.

ABBT205074 Confidential



ABT-773 IV Formulation PPD/HPD Funding Status

- PPD/HPD Collaboration initiated 9/99
- PPD funded Program 01/00-08/00 (\$1.4MM)
 - Formulation development (lactate salt, lyophilized powder)
 - Animal pain models
 - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 (\$0.8MM)
 - Two week Tox study (rat)
 - Clinical supplies for Phase I
 - Stability program
- 2001 funding
 - HPD first pass funding cut for 773 IV (\$7MM)
 - Milestone funding to Phase I Go/No Go (\$1MM)
- Total program development costs 2000 2003 (\$22.5MM)



ABT-773 IV Formulation Animal Pain Study Results

- Assessed 6 prototypes (3 different counter ions at 2 pH levels) vs clarithromycin IV and azithromycin IV
- Animal pain models showed no differentiation among all three compounds
 - Results not conclusive
 - Need to evaluate in humans
- Chose ABT-773 lactate as the prototype to test in Phase I studies based on manufacturability and stability.

ABBT205076 Confidential



ABT-773 IV Planned Clinical Program

With 2001 funding decision in Feb:

Single Dose-rising Phase I study
Multiple Dose Phase I with selected dose
File US IND
Initiate Phase III
- 2 step-down CAP studies (US/Europe)
- 2-3 days dosing
- Two seasons to complete
Filing
Aug/03



ABT 773 IV Program Summary

Comments

- Funding for '01 not available PPD/HPD
- Go/No go could be made after Phase I based on safety profile (pain,QT,GI)
- Milestone funding recommended (\$1MM)
- Assuming Go, '01 budget estimated \$7MM
- IV will help to obtain resistant S. pneumo claim
- Total Program Cost 2000-2003 (\$22.5MM)





ABT-773 Pediatric Formulation Importance to the 773 program

- Increased perception of safety
- Better pricing and acceptance in European markets
- FDA requires studies in pediatrics



ABT-773 Pediatric Program Formulation Objectives

- · Develop coated particle formulae for global use
 - coated particles for Suspension 150mg/5mL & 300mg/5mL
 - coated particles as a dry syrup, sprinkle or sachet.
- Desired Properties
 - Once a Day Dosing
 - Acceptable 'Initial Taste'
 - Minimal 'After Taste'
 - No Unpleasant Mouth-feel
 - Acceptable Color and Flavor
 - No Refrigeration Required.



ABT 773 Pediatric Program Taste Assessment

Sensory Analysis of Uncoated Drugs Summary of Results

The three drug substances can be ranked from most to least bitter as follows:

Drug Substance	Concentration (ppm) Which Exhibits an Initial Bitter Intensity ≤1 (Slight)
ABT-773	0.79
Clarithromycin	4.2
Azithromycin	15

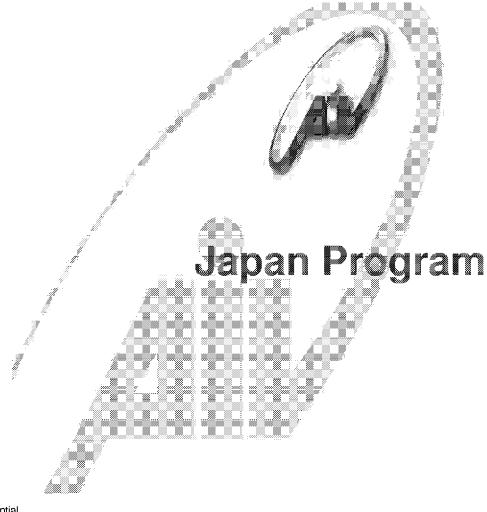
 ABT-773 is approximately five times more bitter than clarithromycin



ABT 773 Pediatric Program Taste Assessment

- The ABT-773 encapsulated prototype #2 may be at risk of dosing compliance problems due to flavor quality.
- Overall ABT-773 Prototype 2
 - Less bitter than Biaxin both initial and after taste
 - More bitter than Zithromax both initial and after taste
- For ABT-773 Prototype 2, the flavoring aromatics and sweetness decay quickly, exposing the bitterness which lingers throughout the aftertaste at or above the "concern" intensity level.

EXHIBIT 608 Part 6





Japan Program Taisho

- Japan development is planned in coordination with Taisho and Dainabot
- Meetings are held at least 3 times a year to review developments
- Taisho funds 10.69% of global development costs and 50% of local Japan costs.
- Bridging strategy is primary plan for development in Japan



Japan Program Clinical Plan

Phase I in Japan

Food Effect Study

<u>Start</u>

Completed

Single and multiple dose study

Completed

Review data (Abbott/Taisho)

April/01

- PK data Japanese vs Caucasian
- Development program strategy

 Present Kiko data and recommend development program May/01

Start Tissue Conc. Study

2Q/01

Confidential

ABBT205086



Japan Program Clinical Plan

- PK similar in Japanese and Caucasians (12/02 filing)
 - Recommend to Kiko same dose in Japan as in ex-Japan
 - Recommend to Kiko one comparative bridging study in CAP (Phase III) and several smaller local studies in skin infections, dentistry, otolaryngology, UTI and pan-bronchiolytis
 - Taisho agreement necessary prior to Kiko meeting
- PK different in Japanese and Caucasians (12/03 filing)
 - Phase II dose ranging study in CAP (Bridging study)
 - Phase III comparative study will be required
 - Full development time line
 - Implications on Taisho cost-sharing

ABT-773 Portfolio Review
December 5, 2000



Agenda

Part 1: General Overview, Tablet

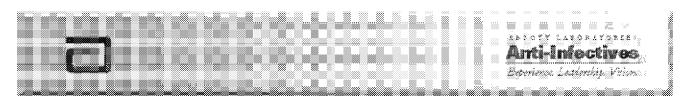
- · Introduction-Carl Craft (5 min)
- Executive Summary-George Aynilian (10 min)
- Anti-Infective Market/Commercial Rationale-Rod Mittag (15 min)
- Microbiology-Bob Flamm (20 min)
- · Tablet Clinical Program
 - Phase II data-Joaquin Valdes (20 min)
 - Phase III clinical plan-Joaquin Valdes (10 min)
- SPD Summary-Ashok Bhatia (10 min)
- · Tablet Key Issues
 - Analysis of QT/Liver data-Dave Morris (20 min)
 - PK profile-Linda Gustavson (10 min)
 - Regulatory-Jeanne Fox (10 min)
 - Timeline risk George Aynilian (5 min)
- Tablet Commercial Profile, Strategy & Financials-Rod Mittag (10 min)



Agenda

Part 2: I.V., Pediatric, Japan, Q&A

- I.V. Program/Issues-Carol Meyer (5 min)
- · Pediatric Progam/Issues-Carol Meyer (5 min)
- · Japan Program/Issues-Carol Meyer (5 min)
- ABT-492 (time permitting)
 - timeline
 - budget
 - rationale
- · Summary-Carl Craft (5 min)
- Q&A



ABT-773 Executive Summary

Management

- Established European Clinical Team (11 dedicated members)
- Plans ongoing to strengthen Japan team
- Completed staffing of Abbott Park team
- Established communication team
- Completed conceptual model of study tracking application (web based)
- Established integrated project management system



ABT-773 Executive Summary

Chemistry

- Exceeded '00 goals for yield, cost/Kg and deliveries
- Task Force implemented modification of 3 steps
- 3 TPMs for intermediates well established
- Prepared package for justifying Step 5 as starting material



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Tablet Formulation

- Scale up operations at AP and IDC on target
- Linkage of materials between scales and sites being established by bioequivalency trials.
- NDA runs and stability were initiated for 08/02 filing.



IV Formulation

Clinical supplies complete. Tox. program ongoing. Phase I planned for 1Q '01.

Pediatric formulation

 Phase I complete with two prototypes. After- taste an issue. Formula optimization required. Pro-drugs under consideration. No funding in '01 plan budget



Preclinical Safety

 Dog model (IV infusion) and Purkenje fiber studies completed as part of effect of drug on QTc. Additional study planned per EOPII meeting with FDA.

Molecular Biology

 Extensive work on ribosomal binding completed. Preliminary results published. Additional studies ongoing.



ABT-773 **Executive Summary**

Clinicals

- Completed Three Phase IIb studies
- Decision Support Analysis completed
- Dose selection 150mg and 150mg bid
- Initiated Phase III program(6 studies, 4 under IND)
- Completed all Investigator's meetings
- Regulatory meetings
 - UK, Germany, France, US

End of Phase II package

- Document sent to FDA X/X
- End of phase II meeting held with FDA 11/26
- Japan bridging study/Kiko Mtg/Repeat Phase I in Japan



Key Events (Nov '00-June '01)

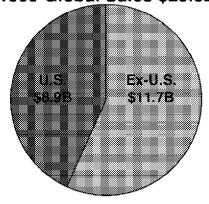
- Initiate Phase III (ABECB, ASP, ABS, CAP)in US/EU
- End of Phase II meeting with FDA(New amendment, informed consent)
- Initiate Japan Phase I program in Japan
- Results of Phase III (CAP/ABS) studies
- Selection of regimen between 150mg QD and 150mg BID for CAP/ABS.
- Set up balance of Phase III studies(CAP/ABS) 4 studies



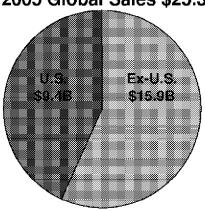
Global Antibiotic Market Sales

Current vs Future Projection





2005 Global Sales \$25.3B

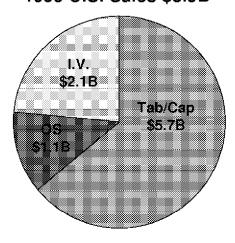


The antibiotic market is a large market and is expected to expand on a global sales basis

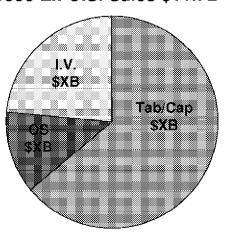


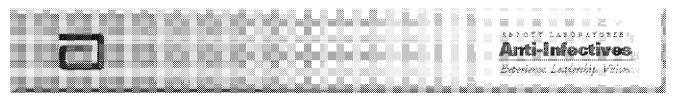
Global Antibiotic Market Sales by Formulation

1999 U.S. Sales \$8.9B

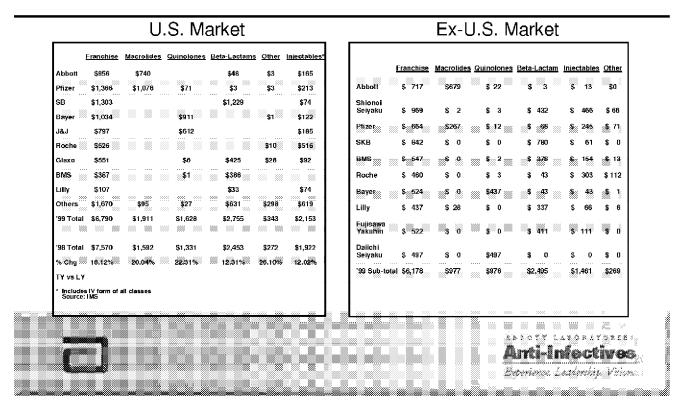


1999 Ex-U.S. Sales \$11.7B

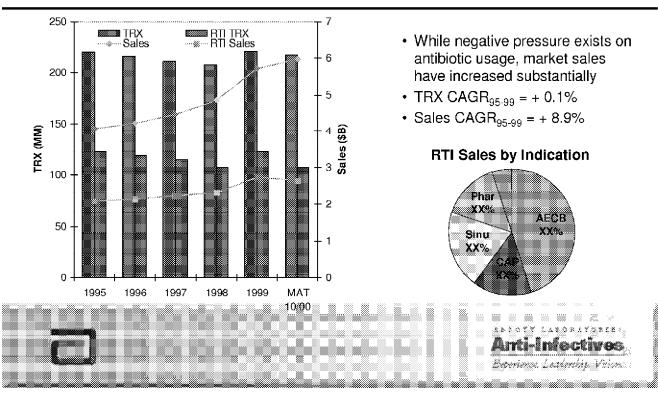




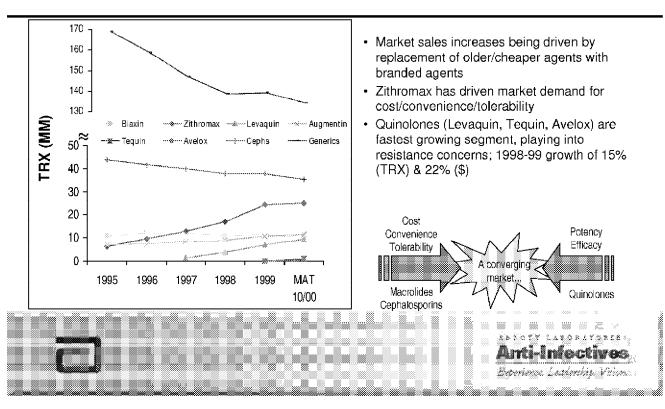
Key Competitors



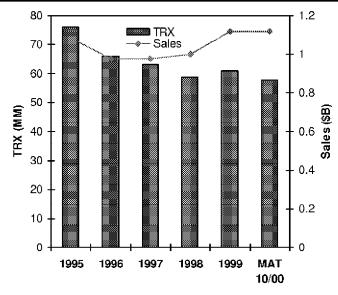
U.S. Tab/Cap Antibiotic Market TRX & Sales Trends



U.S. Tab/Cap Antibiotic Market Product Trends

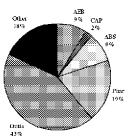


U.S. Pediatric Antibiotic Market TRX & Sales Trends



- TRX CAGR₉₅₋₉₉ = 5.4%
- Sales CAGR₉₅₋₉₉ = + 1.0%
- TRX under greater pressure than Tab/Cap market
- · Recent leveling in sales

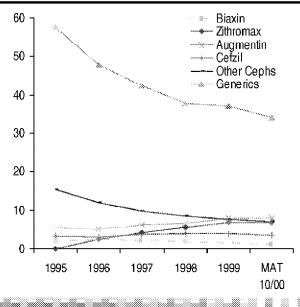
Sales by Indication





U.S. Pediatric Antibiotic Market Product Trends

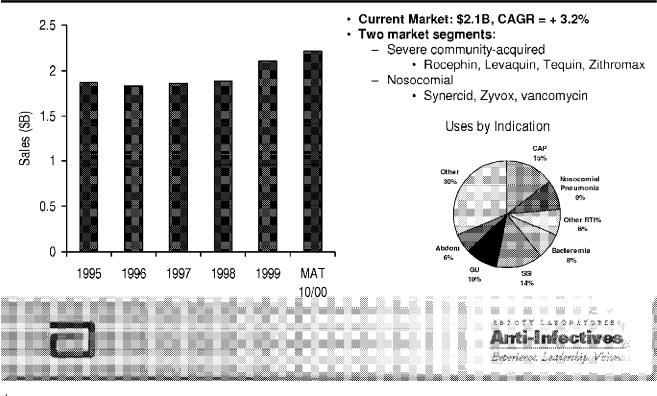
Page 22 of 51



- Market sales increases being driven by replacement of older/cheaper agents with branded agents
- Taste and convenience are key market drivers
- Key branded products (Zithromax, Cefzil) lose patent exclusivity in 2005 timeframe
- May be opportunity for ABT-773, as resistance is substantial in this population; also conveys positive "safety" image to brand

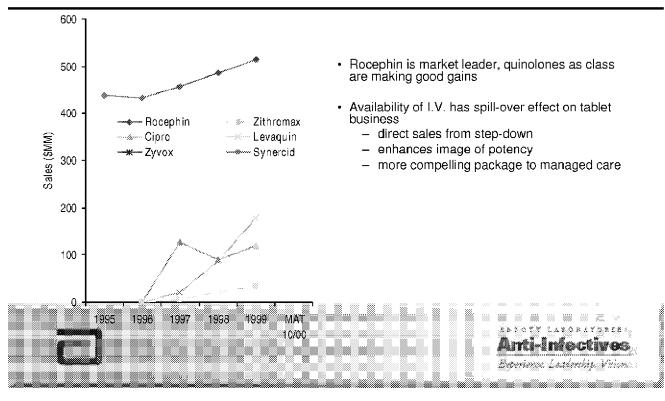


U.S. Injectible Antibiotic Market Sales Trends



U.S. Injectible Antibiotic Market Product Trends

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Global Market Drivers Negative vs Positive Drivers

· Antibiotic Resistance

Increasing sensitivity toward "appropriate use" may have negative impact on usage 👢

Requires new agents to keep ahead of resistant pathogens; substitution of older generic agents with newer branded agents agents

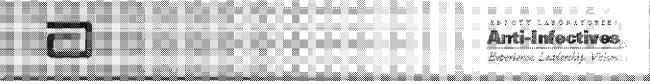
· Patent Expirations

May increase price sensitivity and bargaining power of MCOs 🚇

Use of generic agents tend to decrease over time; obsolescence/resistance may further that trend 1

- Market expansion ex-US 1
- Unmet Need 🖳
 - Overall unmet need relatively low
 - Cost, convenience, tolerability take on added importance
 - Increasing use of "implied efficacy" metrics i.e. MICs, resistance surveillance, AUC/MIC, MPC, kill kinetics
- Competition 🎩
 - 5 NDAs/approvals in last 12 months; Avelox, Tequin, Factive, Spectracef, Ketek, Zyvox
 - Continued discovery/development activity by key competitors
 - High level of promotional activity





· Resistance surveillance

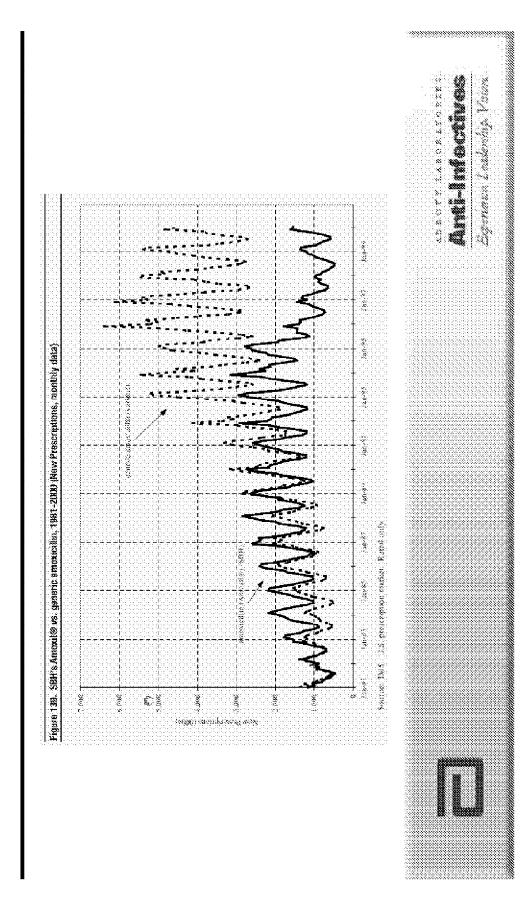


Patent Expirations Expiration & At Risk Sales

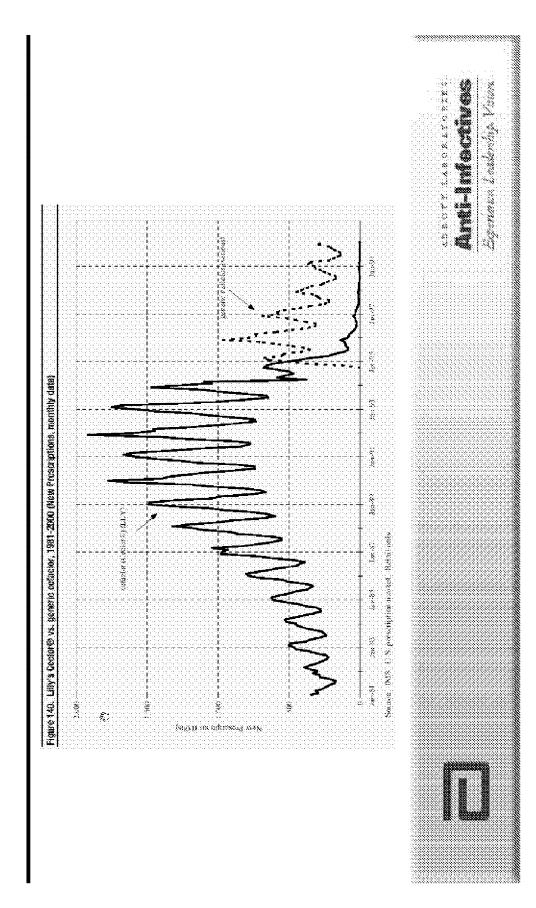
	<u>Year</u>	1999 U.S. Sales (\$MM)
Ceftin	2003	\$425
Cipro	2003	\$1,023
Biaxin	2005	\$756
Cefzil	2005	\$357
Levaquin	2005	\$708
Zithromax	2005	\$1,111

\$5,540

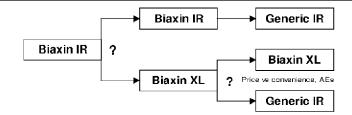




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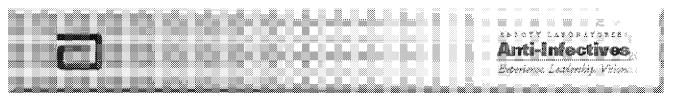


Biaxin Patent Expiration Biaxin/773 Scenarios

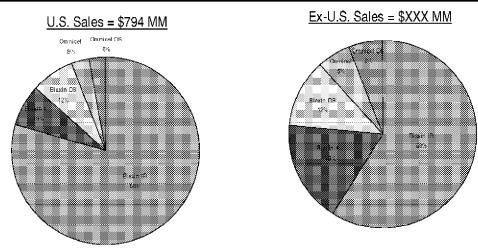


		XL==>	Generic Cor	version
		Low	Med	High
/ersion	Low	?	C	O
IR ==> XL Conversion	Med		?	O
B=↓	High			?

C = Convert Biaxin to ABT-773 Assumes high conversion rate of IR to generics



Abbott Anti-Infective Franchise 2001 Plan



The global Anti-Infective portfolio is heavily dependent upon Biaxin; ABT-773 represents a key program given the Biaxin patent expiration in 2005



ABT-773 Profile

	Current Profile
Dosing	150 mg QD x 5 d for ABECB & pharyngitis (1-pack) 150 mg QD or BID x 10 d for CAP & ABS (2-pack if QD)
Efficacy	ABECB: 87% Cure, 86% Eradication (150 mg QD) ABS: 89% Cure, 77% Eradication (150 mg QD) CAP: XX% Cure, XX% Eradication (300 mg QD) Pharyngitis: No clinical data, need > 85% for indication
Adverse Events (150 mg QD)	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%
Resistance Claim	Being pursued, dependent on resistance prevalence/recovery/efficacy & availability of I.V.



ABT-773 Profile vs Biaxin XL

	ABT-773	Biaxin XL
Dosing	ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d	All regimens 2 x 500 mg QD ABECB: 7 d CAP: 7 d ABS: 14 d
Efficacy	ABECB: 87% Cure, 86% Erad ABS: 89% Cure, 77% Erad CAP: XX% Cure, XX% Phar: No data	ABECB: 83-86% Cure, 86-92% Erad ABS: 85% Cure, NA Erad CAP: 89% Cure, 89% Erad
Adverse Events	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%	Taste perversion: 6% Diarrhea: 6% Nausea: 3% Vomiting: 1%
Resistance Claim	Being pursued	Under exploration



Key Commercial Challenges

• 150 mg QD vs 150 mg BID

- 150 mg QD may prove efficacious in CAP/ABS ==> uniform QD dosing; however, limited 150 mg QD data currently exists, hence risk of BID dosing for CAP/ABS
- Even if 150 mg QD efficacious, this regimen could receive regulatory challenge, particularly among ex-U.S. agencies ==> QD and BID development programs, increased
- PK
 - Negative implications for efficacy as well as resistance development
- · H. flu eradication
 - dose-defining pathogen, limited number of data points to date
 - a strength of quinolones
- · Tolerability may be sub-optimal
 - diarrhea and taste perversion
- · 2nd to market ketolide
 - Aventis ketolide Ketek (telithromycin), FDA advisory 1/29



ABBT205116 Confidential

Phase II Data: 150 mg QD vs 300 mg QD

			Phase IIb Data: Intent-to-treat							
			Bro.	nchitis	C	AP	Sinu	ısitis	Г	'otal
Clinical Cure	15	0 mg QD	85%	104/123	4		82%	72/88	83%	176/211
Chineal Cure	3(Omg QD	83%	107/129	84%	¥0/95	80%	72/90	82%	159/314
	பசிய	150 mg QD	89%	17/19	-		60%	3/5	83%	20/24
Bacteriological	H. flu	30thing QD	.81%	17#21	100%	9/9	100%	7.77	89%	33/37
Cure	S.	150 mg QD	77%	10/13			100%	3/3	81%	13/16
	рпеито	300 mg QD	90%	9/10	82%	14/17	100%	8/8	89%	31/35

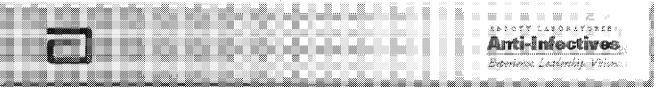


- Ketek (telithromycin, Aventis) will be first-to-market ketolide
- · U.S.
 - Filed with FDA March 2000
 - FDA advisory 1/29
 - Expected approval 1Q01
- Ex-U.S.
 - Package submitted to EMEA as centralized filing in March 2000
 - Rapporteur = Sweden
 - Co-rapporteur = Portugal
 - Expected approval 1Q01
- Phase II in Japan (source: IMS World R&D Focus)



Ketek Summary Profile Summary

- 800 mg QD for all indications
- AECB (5 d), CAP (7-10d), sinusitis (5d), pharyngitis (5d)
- High rate of diarrhea (10-20%), nausea (10%), but no taste perversion
 - statistically greater diarrhea vs trovafloxacin in phase III study
- · Comparable levels of efficacy to comparators (see appendix for full clinical summary)
 - 74%-95% clinical cure
 - 69%-94% overall eradication
 - H. flu eradication is varied, with two CAP studies having 75% and 78% eradication; an AECB and sinusitis study had H. flu eradication of 88% and 100% respectively
- · Liver function elevation
 - mentioned at ICAAC99, but Aventis claimed no clinically relevant impact at ICAAC2000; a CAP study references a 11.3% incidence of abnormal liver function, though the severity is unknown
- · QTc prolongation: Aventis maintains no clinically relevant impact
- · High COGS based on SPD pricing on intermediate
 - estimated telithromycin bulk drug cost of ~\$6,000/kg at launch vs \$3,000 for 773 at launch
 - may limit pricing flexibility
- Competitive intelligence suggests 14 penicillin resistant isolates submitted, same number as Levaquin (potential for pen-resistance claim, which Levaquin was granted)
 - eradication rate with these isolates unknown, important factor in FDA decision



Ketek Summary ABT-773 Comparison

	ABT-773	Ketek
Dosing	ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d	All regimens 2 x 400 mg QD ABECB: 5 d Phar: 5 d CAP: 7-10 d ABS: 10 d (or 5 d?)
Efficacy	ABECB: 87% Cure, 86% Erad ABS: 89% Cure, 77% Erad CAP: XX% Cure, XX% Phar: No data	ABECB: 86-89% Cure, 69-88% Erad ABS: 76-91% Cure, 86-91% Erad CAP: 91-93% Cure, 86-94% Erad Phar: 93-95% Cure, 84-91% Erad
Adverse Events	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%	Taste perversion: Not reported Diarrhea: 10-20% Nausea: 10% Liver, QTc: ???
Resistance Claim	Being pursued	Submitted in NDA



Filed 03/10/2008

ABT-773 Strengths vs Ketek

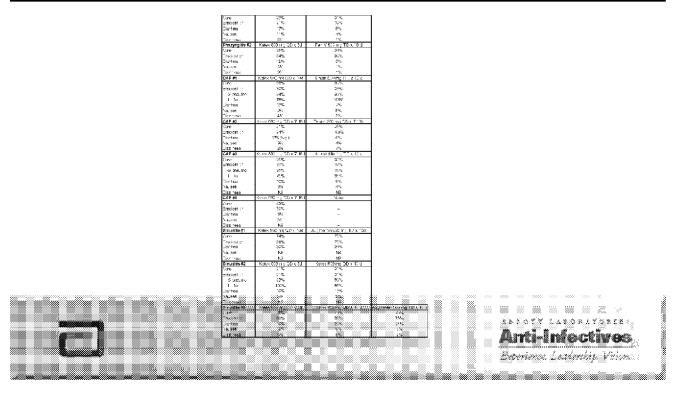
- ABT-773 is considerably more potent than telithromycin against:
 - resistant and susceptible strains of S. pneumo
 - atypicals
 - H. flu (based on in vivo animal models)
- · Lower rate of adverse events, particularly diarrhea
- 1 tab per dose vs 2
- · Mechanistic advantages
 - faster binding to ribosome, slower release from ribosome, perhaps additional binding site(s)
- · Potential for greater pricing flexibility

ABT-773 Threats/Issues vs Ketek

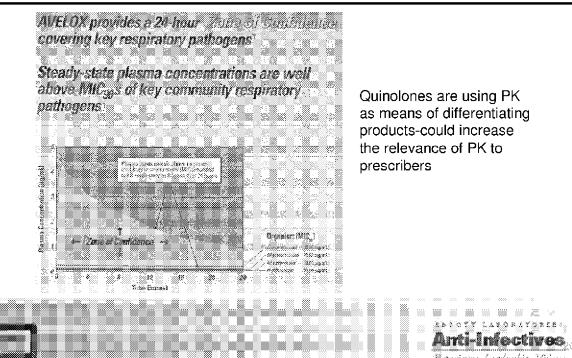
- · 2nd to market
- · Potential for BID dosing in CAP and/or sinusitis
- · ABT-773 clinical/safety data at 150 mg QD based on relatively few data points
- · PK profile



Ketek Summary Clinical Data

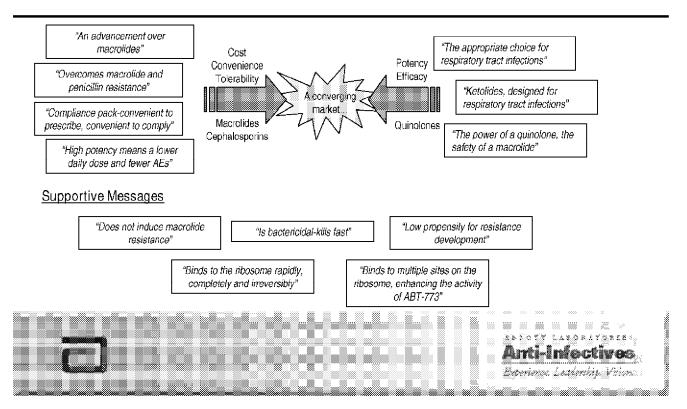


PK Issue



Key Commercial Messages

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Communications Strategy

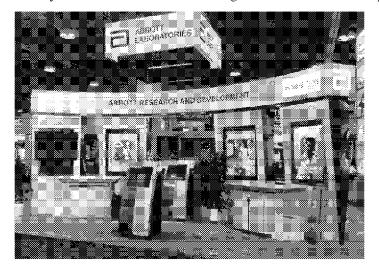
Messages

- microbiological data (resistance, the better ketolide)
- PK (no food effect, favorable drug-drug)
- Mechanism (ribosome binding, PAE, etc., "explanation" for ketolide activity, defense of dose selection
- Clinical data
- Implementation
 - Strategic initiation of studies to support desired messages, monthly strategy meetings, intranet under development to manage activities/history
 - Scientific meetings (51 posters at 6 scientific meetings in 1999-2000)
 - Publications (10 publications in 2000)
 - Medical Liaisons(sp)
 - VIP Visits



ICAAC 2000

International Conference on Antimicrobial Agents and Chemotherapy, Toronto



See you at ICAAC 2001, in Chicago, Illinois!!



Forecast Assumptions

	<u>US</u>	<u>Europe</u>	<u>Japan</u>		
Dosing	150 mg QD dosing all indications AECB & Phar, 5 d CAP & ABS, 10 d				
Efficacy	Comparable to other agents				
AEs	Comparable to Biaxin XL				
COGS	\$3,000/kg at launch				
AWP/Day	\$8.60				



Forecast

	<u>U.S.</u>	<u>Europe</u>	<u>Japan</u>	ROW	<u>Total</u>
Peak Sales	\$432MM				
Peak TRX Share	7.5%				N/A
NPV @12.5%					

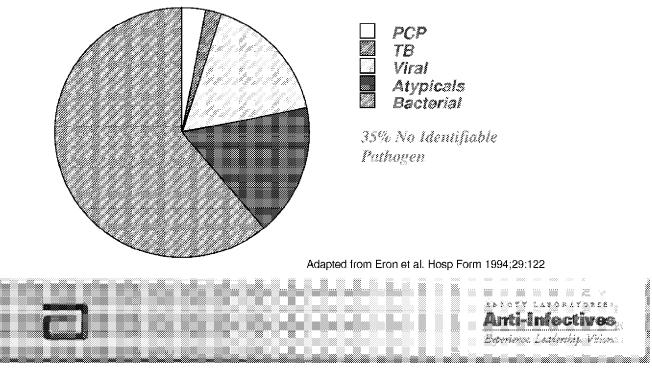


· Ketolides are a Novel Class of Antimicrobial

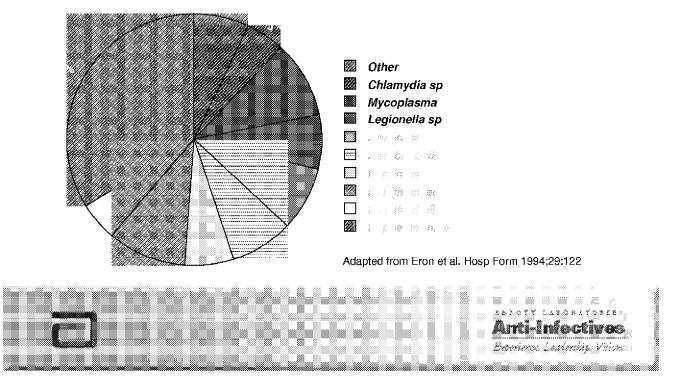
- Active vs.key respiratory tract infection pathogens to include macrolide resistant streptococci
- Bactericidal activity
- · Prolonged post antibiotic effect
- · Reduced resistance development



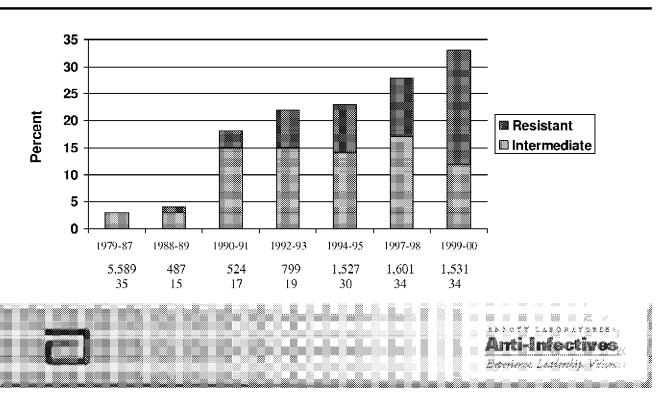
Microbiology Community-Acquired Pneumonia in Adults



Microbiology Bacterial Causes of Community-Acquired Pneumonia in Adults



Microbiology
Penicillin resistance with Streptococcus pneumoniae in the United States



Microbiology

US Respiratory Surveillance Studies, Penicillin Susceptibility in S. pneumoniae

Year	1994-95	1997-98	1999/2000
Season	Winter	Winter	Winter
No. of centers	30	34	34
No. of isolates	1,528	1,601	1531
No. % intermediate	216 (14. l)	278 (17.4)	194(12.7%)
No. % resistant	145 (9.6)	196 (12.2)	29 (21.5%)

Dr. G. Doern, Univ. of Iowa



EXHIBIT 608 Part 7

Microbiology Antimicrobial Resistance Rates among S. pneumoniae

	1994-95	1997-98	1999-2000
Antimicrobial Agent	N=1527	N=1601	N=1531
Macrolide	10.0	18.9	25.9
Tetracycline	7.5	12.9	16.4
Chloramphenicol	4.3	7.2	8.4
Clindamycin	Na	5.6	8.8
TMP/SMX	18.0	20.4	30.3

Dr. G. Doern, Univ. of Iowa



Microbiology

Rates of Resistance of Non- β -Lactam Antimicrobials with Streptococcus pneumoniae
Based on Penicillin Susceptibility Category

Percentage Resistance Among

<u>Antimicrobial</u>	PenS-(n=1,008)	PenI(n=194)	PenR(n=1,531)
Macrolides	5.6	43.3	78.1
Clindamycin	1.4	19.1	25.2
Chloramphenicol	1.0	13.9	27.7
Tetracycline	3.1	32.0	48.0
TMP/SMX	7.6	39.2	94.5

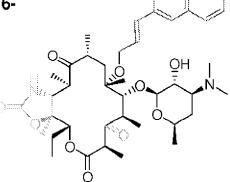
[n=1,531, 34 U.S. centers, 1999-2000], Doern et al

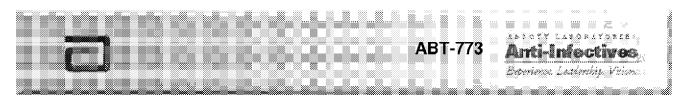


Microbiology ABT-773 Structure/SAR

•Quinolylallyl propenyl moiety at the 6-0 -position

- •Keto group at the 3-position
- •Carbamate group at the 11, 12-position





Microbiology Macrolide Resistance Types

Microbiology Overview

- Two major macrolide resistance mechanisms in streptococci and staphylococci:
 - Ribosomal methylase blocks macrolide binding to target
 - Macrolide and clindamycin MIC >16 μg/mL
 - Macrolide efflux actively pumps macrolide out of cell
 - Macrolide MIC 1-32 µg/mL; clindamycin MIC ≤ 0.25 µg/mL

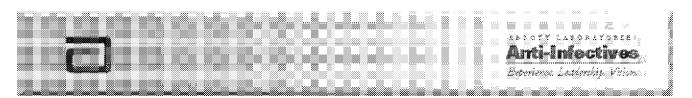


Microbiology
Resistance Mechanisms Prevalence in S. pneumoniae Clinical Isolates

Genotype	U.S. 1994-95¹ r⊨114	U.S. 1997-98 ² n=302	Canada ³ n=147	Europe ⁴	Japan ⁵ n=62
ermB	32%	29%	39%	97%	40%
mefE	6 1 %	71%	56%	3%	43%
mef/erm	5%	_	<1%	-	16%
Unknown	2%	_	6%	-	0%

¹Shortridge, et al. *CID*. 1999; 29:1186-8.

⁵Nishijima et. al.JAC.1999.43:637-643



² Doern, et al. *EID*. 1999; 5(6).

³ Johnston, et al. AAC. 1998; 42:2425-26.

⁴Schmitz et. al.JAC.1999.43:783-92

Microbiology ABT-773 Activity, University of Iowa Resistance Survey

Isolates by Erythromycin MIC

	· <0	romycin MIC Er 0.5 _µ g/ml (n=1299)		Erythromycin MIC 1-32 _µ g/mI (n=222)		Erythromycin MIC ≥64 μg/mI (n=80)	
Drug	MIC ₉₀	MIC range	MIC90	MIC range	MIC ₉₀	MIC range	
A8T-773	_≤ 0.0 0 8	≤0.008 - 0.12	0.03	≤0.008 - 0.5	0.12	≤0.008 - 0.5	

1997-1998 Survey, Brueggemann et. al. 2000. AAC. 44:447-449



Microbiology
ABT-773 Activity, University of Iowa Resistance Survey

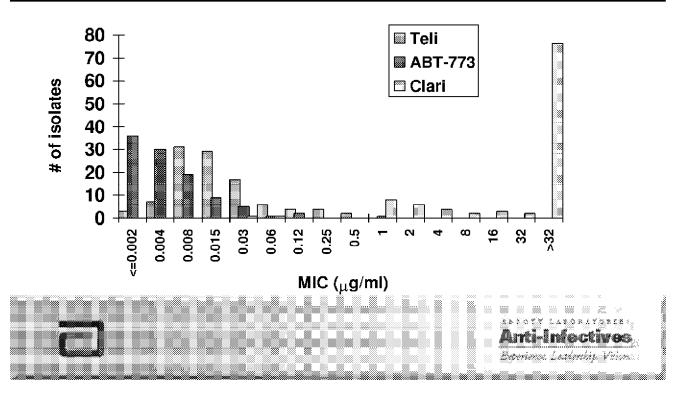
Isolates by Penicillin MIC

		enicillin Susceptible MIC $_{\leq}0.06$ $_{\mu}$ g/ml (n=1127) Penicillin Intermediate MIC 0.12-1.0 $_{\mu}$ g/ml (n=278)		Penicillin Resistant MIC _≥ 2.0 _μ g/ml (n=196)		
Drug	MIC ₉₀	MIC range	MIC ₉₀	MIC range	MIC ₉₀	MIC range
ABT-773	≤0.008	≤0.008 - 0.5	0.03	≤0.008 - 0.5	0.12	≤0.008 - 0.25
Ery	0.06	≤0.03 - >64	>64	≤0.03 - >64	>64	≤0.03 - >64

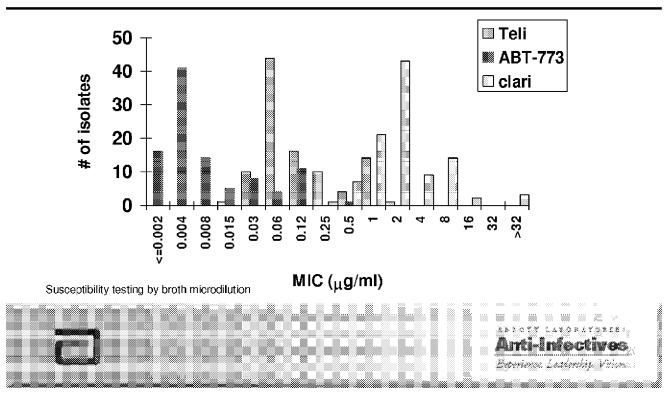
1997-1998 Survey, Brueggemann et. al. 2000. AAC. 44:447-449



Microbiology MIC Distribution of S. pneumoniae methylase⁺ strains



Microbiology MIC Distribution of S. pneumoniae efflux* strains



Microbiology In vitro Activity, S. pyogenes

MIC₉₀ Range in μg/ml

Organism	Macrolide susceptible	Macrolide resistant
ABT-773	≤0.016 - 0.03	0.06 - 0.12
Erythromycin	0.06 - 0.12	8 - 16

References:

Barry et al ICAAC 1999 #2144 Dubois et al. ICMASKO 2000 #2.15 Singh et al. ICMASKO 2000 #2.14



Microbiology

In vitro Activity , Haemophilus, Moraxella spp.

MIC_{90} Range in $\mu\text{g/mI}$

Organism	H. influenzae	M. catarrhalis
ABT-773	2 - 4	0.06 - 0.25
Azithromycin	2 - 4	0.06 - 0.12
Erythromycin	8 - 16	0.25 - 0.5

References:

Barry et al ICAAC 1999 #2144 Hoellman et al ICAAC 1999 #2140 Brueggemann et al. 2000.AAC.44:447-449 Shortridge et. al.1999. ICAAC



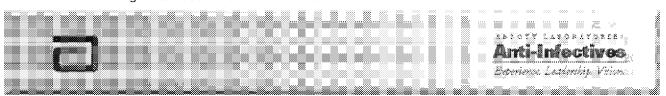
Microbiology

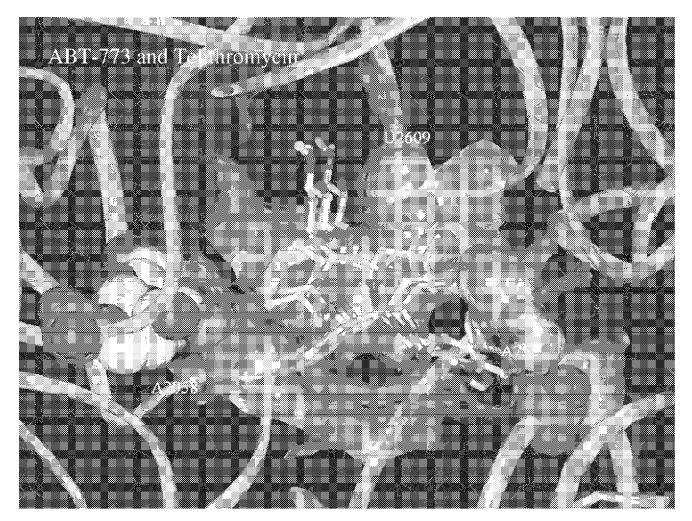
Comparison of activity vs. respiratory atypical pathogens

MIC_{90} in $\mu g/mI$

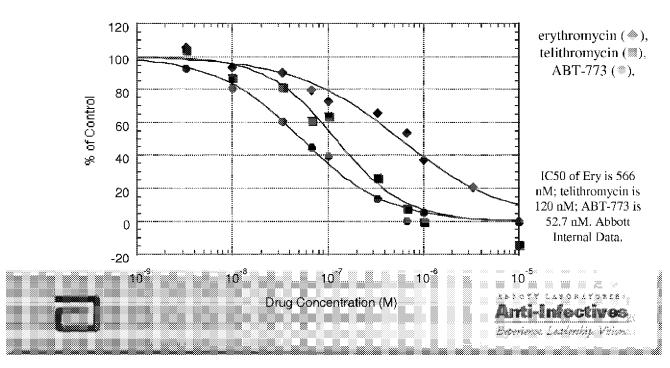
Organism	ABT-773	Ery
Legionella spp. 1 (105)	0.03-0.12	0.25-1.0
M. pneumoniae ² (18)	≤ 0.0005	0.008
C. pneumoniae ³ (20)	0.015	0.06

¹Victor Yu, ICAAC, 2000. Strains tested: *L. pneumophila* serogroup 1 (68), *L. pneumophila* other serogroups (28), *Legionella* spp other than pneumophila (10). ².Nilius et al. ECCMID 1999. ³ Strigl et. al.2000. AAC.44:1112-1113

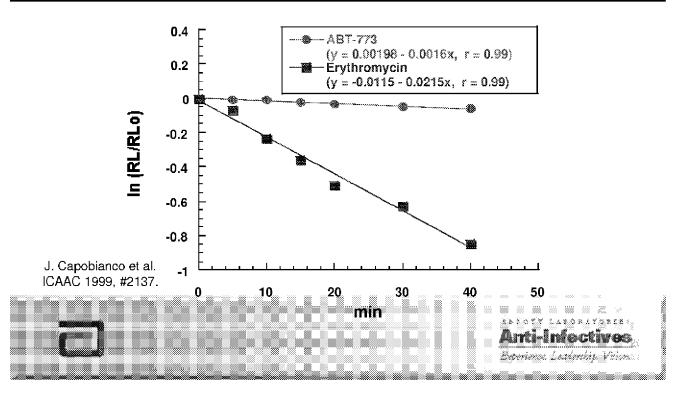




Microbiology
Ribosome Binding, Susceptible S. pneumoniae



ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



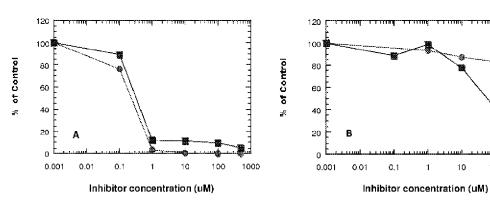
Microbiology Inhibition of Transcription / Translation

100

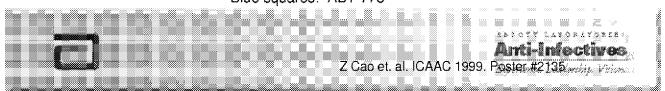
Page 17 of 51

S30 from susceptible S. pneumoniae

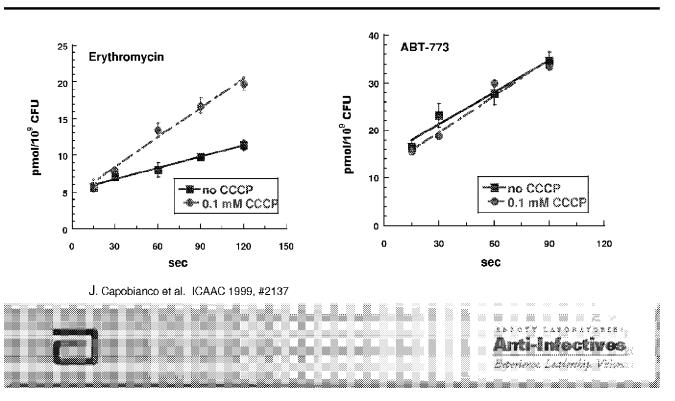
S30 from resistant S. pneumoniae



Red circles: erythromycin Blue squares: ABT-773

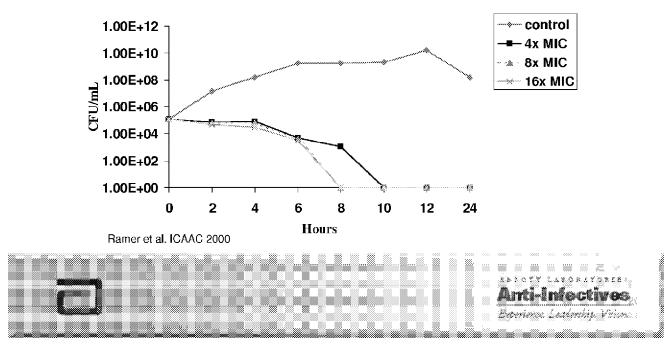


Microbiology
ABT-773 Accumulation in efflux+ strain, with and without pump inhibitor (CCCP)

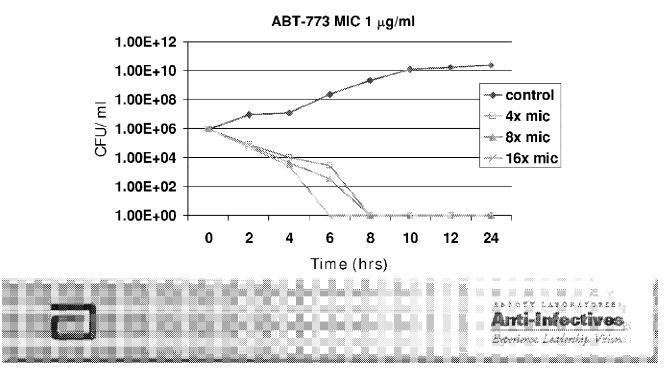


Microbiology Bactericidal Activity, S. pneumoniae

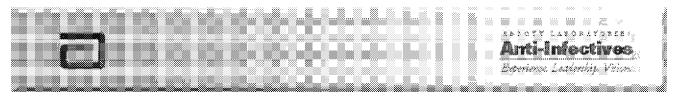
Susceptible S. pneumoniae; ABT-773 MIC 0.002 $\mu g/ml$



Microbiology Bactericidal Activity, H. influenzae



- · After removal of drug the bacterial growth rate is inhibited
- · Justification for dosing regimen such as QD vs. BID
- · Addresses resistance development issues
- · In vitro
 - S. pneumoniae
 - 8 strains
 - mean PAE ABT-773 ≥ 6.1 hr
 - mean PAE ery 3.8hr
 - H. influenzae
 - 5 strains
 - mean PAE ABT-773 <u>></u>6.1 hr
 - mean ery PAE 3.8 hr

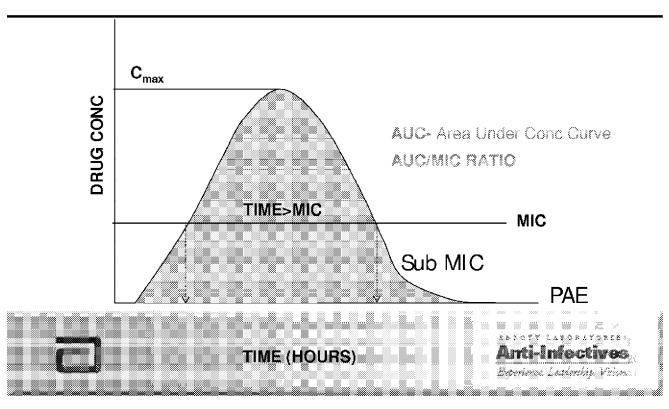


Microbiology Resistance Development

- · Occur by mutation
 - Quinolone resistance in GyrA and ParC
- · Acquired from another bacterium
 - Methylase
 - Elllux
- S. pneumoniae
 - In vitro single step mutation frequency (8XMIC)
 - 1 S. pneumoniae (S) <5.6 X10⁻¹⁰
 - 1 S. pneumoniae mef <2.6 X 10⁻¹²
 - 2 S. pneumoniae ermB 3.5 X 10⁻¹⁰-<9.4X10⁻¹¹
 - Mutation frequency for rifampicin (8XMIC)
 - 4 S. pneumoniae 1.2 X10⁻⁶ to 3.0 X10⁻⁷
 - No difference in mutation rate if macrolide resistant or susceptible
 - Low potential for resistance development



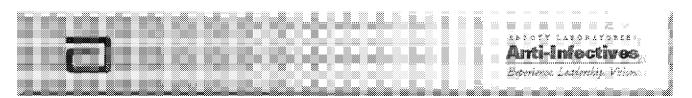




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Antibiotic exposure needed for efficacy against S. pneumoniae in animal models

- AUC/MIC is best predictive parameter for ketolides
- Rat lung model of pneumonia with S. pneumoniae
 - QD an AUC 0-24 ug-h/ml of 0.4-1.0 for an $MIC_{\rm go}$ of 0.12
 - BID an AUC 0-24 ug-h/ml of 0.1-0.4 for an MIC_{90} of 0.12
- Lethal mouse model of pneumonia AUC 0-24 of <3-6 ug.h/ml



Neutropenic mouse thigh model

- S. pneumoniae
 - 6 macrolide susceptible, 8 macrolide resistant
 - 10^{5,8-7,4} CFU/ thigh
 - ABT-773 dose 0.023-24 mg/kg/day Q6 h
 - · Net bacteriostatic effect over 24 hrs is measured

Andes, D.R. and W.A. Craig. ICAAC 2000.



• Neutropenic mouse thigh model- S. pneumoniae

- 24hr AUC/MIC is best PK/PD predictor
- Prolonged PAEs with concentration dependent killing
 - up to 11 hrs
- Magnitude of AUC/MIC is not significantly altered by macrolide resistance with strains with MICs $\,$ as high as $0.5\mu g/ml$

Andes, D.R. and W.A. Graig. ICAAC 2000



· Mouse lethal pneumonia model

- S. pneumoniae-2 strains
 - eryS
 - eryR
- immunocompetent mice
- infected with 104-5 CFU
- treatment 6 or 12 hr post-infection
- subcutaneous dosing
- BID treatment for 3 days

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAC 2000.



- vs. macrolide susceptible

- Ery/ABT-773 MIC 0.015/0.015 ug/ml
 - 100% survival with 3 days of treatment at s.c. 6.25mg/kg
- vs. macrolide resistant
 - Ery/ABT-773 MIC 1024/0.03 ug/ml
 - 93% survival with 3 days of treatment s.c. at 12.5 mg/kg
 - » infected mouse single dose 12.5 mg/kg- AUC 0-24 ug•h/ml 3.08+/- 0.32)

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAC 2000.



- Suggests total daily AUC 0-24 ug.h/ml of <3-6 is sufficient for pneumonia
 - · ketolide is active vs macrolide resistant strain unlike erythromycin
 - no resistant mutants emerged vs ABT-773 but did for erythromycin

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAC 2000.



Microbiology Summary

Page 30 of 51

- Active vs. key respiratory pathogens including macrolide resistant streptococci
- Bactericidal
- Extended PAE
- Low rate of resistance development in vitro and in vivo
- AUC/MIC best predictor of outcome
 - Exposure of <1ug.h/ml AUC_{24} for mild to moderate pneumonia model and AUC_{24} ug.h/ml <3-6 for more severe model



Phase II Clinicals
Joaquin Valdes



Phase II Clinicals Program Summary

Study	Study Drug Dose/Duration	Patient Numbers/location
M99-048 Phase IIb, Double blind Acute Bacterial Exacerbation of Chronic Bronchitis	ABT-773 150, 300 or 600 mg OD Duration: 5 days	N = 384 US, Germany, France, Italy, Spain, UK, Chile
M99-053 Phase Ilb, Double-blind Acute Sinusitis	ABT-773 150, 300, or 600 mg OD Duration: 10 days	N = 292 US, Finland, Greece, Chile
M99-054 Phase Ilb, Double-blind Community Acquired Pneumonia	ABT-773 300 or 600 mg OD Duration: 7 days	N = 187 US, Germany, France, Italy, Spain, Poland, South Africa



Acute Bacterial Exacerbation of Chronic Bronchitis M99-048 Clinical Response

		150 mg		300 mg		600 mg
Clin and Bact. Eval	84%	(42/50)	88%	(49/56)	94%	(59/63)
Clin Eval	87%	(98/113)	90%	(105/117)	90%	(101/112)
IΠ	85%	(104/123)	83%	(107/129)	83%	(106/128)



Acute Bacterial Exacerbation of Chronic Bronchitis M99-048 Bacteriological Response

Clinically and Bacteriologically Evaluable

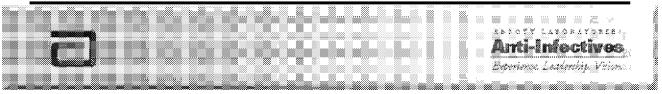
	150mg	300mg	600mg
S. pneumoniae M. catarrhalis H. influenzae	83% (10/12) 80% (8/10) 94% (17/18)	90% (9/10) 92% (12/13) 89% (17/19)	100% (13/13) 91% (10/11) 83% (19/23)
Overall	88% (35/40)	91% (38/42)	89% (42/47)



Acute Bacterial Exacerbations of Chronic Bronchitis M99-048 Adverse Events

All Adverse Events

		150 mg		300 mg		600 mg
GI and Taste						
Taste Perversion	6%	(7/126)	19%	(25/129)	29%	(37/129)
Diarrhea Nausea Vomiting Nausea and Vomiting	13% 7% 2% 0	(16/126) (9/126) (3/126)		(15/129) (17/129) (4/129) (1/129)	30%	(27/129) (38/129) (14/129) (5/129)
Abdominal Pain	4%	(5/126)	4%	(5/129)	4%	(5/129)



Community-Acquired Pneumonia M99-054 Clinical Response

	300 mg	600 mg
Clin and Bact. Eval	92% (54/59)	82% (47/57)
Clin Eval	92% (72/78)	80% (56/70)
ITT	84% (80/95)	73% (65/89)



Community-Acquired Pneumonia M99-054 Radiographic Response

(Resolution/Improvement)

	300 mg	600 mg	
Clin and Bact. Eval	100% (56/56)	89% (48/54)	
Clin Eval	99% (73/74)	88% (57/65)	
ITT	84% (80/95)	72% (64/89)	



Community-Acquired Pneumonia M99-054 Bacteriological Response

Clinically and Bacteriologically Evaluable						
		300 mg		600 mg		
S. pneumoniae	87%	(13/15)	100%	(7/7)		
M. catarrhalis	75%	(6/8)	50%	(2/4)		
H. influenzae	100%	(9/9)	72%	(13/18)		
M. pneumoniae	93%	(13/14)	93%	(14/15)		
C. pneumoniae	95%	19/20)	79%	(19/24)		
L. pneumoniae	100%	(3/3)	100%	(2/2)		
Overall	91%	(63/69)	81%	(57/70)		



Community-Acquired Pneumonia M99-054 Adverse Events

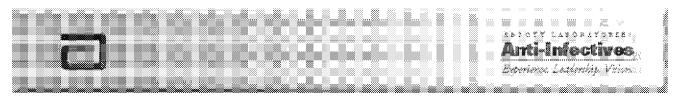
All Adverse Events

		300mg		600mg
GI and Taste				
Taste Perversion	17%	(16/95)	26%	(24/92)
Diarrhea	14%	(13/95)	19%	(17/92)
Nausea	12%	(11/95)	22%	(20/92)
Vomiting	10%	(9/95)	15%	(14/92)



Sinusitis M99-053 Clinical Response

	150 mg	300 mg	600 mg
Clin Eval	89% (70/79)	83% (70/84)	71% (59/83)
ITT	82% (72/88)	80% (72/90)	67% (59/88)



Sinusitis M99-053 Radiographic Response

(Resolution/Improvement)

	150 mg	300 mg	600 mg
Clin Eval	86% (68/79)	86% (71/83)	78% (59/76)
ІТТ	81% (71/88)	81% (73/90)	67% (59/88)



Sinusitis M99-053 Bacteriological Response

Clinically and Bacteriologically Evaluable

	150mg	300mg	600mg
S. pneumoniae	3/3	8/8	9/12
M. catarrhalis	8/9	3/4	4/4
H. influenzae	3/5	7/7	5/7
S. aureus	1/1	1/1	3/4



Sinusitis M99-053 Adverse Events

All Adverse Events

	150 mg	300 mg	600 mg
GI and Taste			
Taste Perversion	1% (1/97)	14% (14/98)	27% (26/97)
Diarrhea Nausea Vomiting	6% 6/97) 3% (3/97) 1% (1/97)	6% (6/98) 12% (12/98) 6% (6/98)	17% (16/97) 26% (25/97) 17% (16/97)

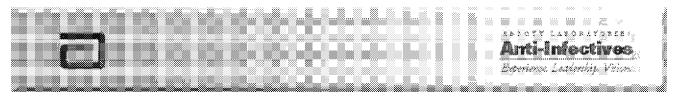


Insert cure/erad/AE summary table



ABECB, CAP, AMS M99-048, M99-054, M99-053 Clinical Response

	150 mg	300 mg	600 mg
Clin and Bact. Eval	84% (42/50)	90% (103/115)	88% (106/120)
Clin Eval	88% (168/193)	88% (247/279)	81% (216/265)
ITT	83% (176/211)	82% (259/314)	75% (230/305)



ABECB, CAP, AMS M99-048, M99-054, M99-053 Bacteriological Response

Clinically and Bacteriologically Evaluable

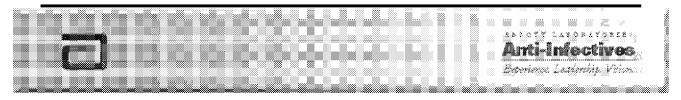
	150mg	300mg	600mg
S. pneumoniae M. catarrhalis H. influenzae	87% (13/15) 84% (16/19) 87% (20/23)	91% (30/33) 84% (21/25) 94% (33/35)	91% (29/32) 84% (16/19) 77% (37/48)
Overall	86% (49/57)	90% (84/93)	83% (82/99)



ABECB, CAP, AMS M99-048, M99-054, M99-053 Adverse Events

All Adverse Events

	150	mg	300 mg	600 mg
GI and Taste				
Taste Perversion	4% (8/	223) 17 %	(55/322)	27 % (87/318)
Diarrhea Nausea Vomiting	5% (12/	223) 12%	(40/322)	19% (60/318) 26% (83/318) 14% (44/318)



Phase II summary

- ABT-773 was equally effective at 150 mg QD and 300 mg QD doses in ABECB and ABS
- · ABT-773 was efficacious against all target pathogens
- All doses were safe; 150 mg QD was best tolerated for GI events and taste perversion
- 150 mg QD will be evaluated in comparative studies of ABECB and pharyngitis in phase III
- 150 mg QD and 150 mg BID will be evaluated to select a regimen for CAP and ABS

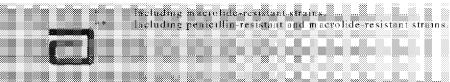


Phase III Clinical Program Joaquin Valdes



Proposed Indications and Treatment Duration

	Dosage	Duration
Infection	(QD)	(days)
Pharyngitis/Tonsillitis due to		
S. pyogenes*	150 mg	5
Acute bacterial sinusitis due to		
H. $influenzae$	150 mg (or BID)	10
M. $catarrhalis$	150 mg (or BID)	10
S. pneumoniae**	150 mg (or BID)	10
Acute bacterial exacerbation		
of chronic bronchitis due to		
H. influenzae	150 mg	5
H. parainfluenzae	150 mg	5
$\it M. catarrhalis$	150 mg	5
S. pneumoniae ** "	150 mg	5
Community-acquired		
pneumonia due to		
C. pneumoniae	150 mg (or BID)	10
H. influenzae	150 mg (or BID)	10
L. pneumophila	150 mg (or BID)	10
M. pneumoniae	150 mg (or BID)	10
S. pneumoniae**	150 mg (or BID)	10





Phase 3 Studies

Studies starting in year 2000:

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Location
M00-223	Pharyngitis	150 mg QD 5 days	Penicillin V	260	US (IND)
M00-222	Pharyngitis	150 mg QD 5 days	Penicillin V	260	EU (Non-IND)
M00-216	ABECB	150 mg QD 5 days	Azithromycin	300	US, Canada IND
M00-217	ABECB	150 mg QD 5 days	Levofloxacin	250	EU (Non-IND)



EXHIBIT 608 Part 8

Phase 3 Studies

Studies starting in year 2000 (Cont.):

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Location
M00-225	Sinusitis	150 mg QD <i>vs.</i> 150 mg BID 10 days	None	600	US, EU (IND)
M00-219	CAP	150 mg QD <i>vs</i> . 150 mg BID 10 days	None	800	US, Canada, EU (IND)



Phase 3 Studies

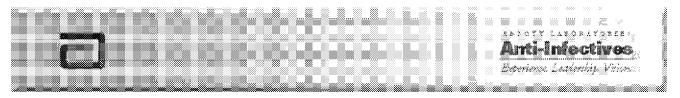
Studies starting in year 2001:

Study	Indication	Comparator	Number ABT-773 Subjects	Location
M00-221	CAP	Levofloxacin	225	US, Canada (IND)
M00-220	CAP	Augmentin or Amoxicillin	250	EU (Non-IND)
M00-226	Sinusitis	Augmentin	225	US, Canada (IND)
M00-218	Sinusitis	Augmentin or Quinolone	250	EU (Non-IND)



Proposed Claim for Macrolide or Penicillin Resistant Bacteria and Atypicals

Claim	Supporting Data	
Macrolide-resistant S. pneumoniae	15 isolates worldwide from Phase 3 CAP and ABECB	
Penicillin-resistant <i>S. pneumoniae</i>	15 isolates worldwide from Phase 3 CAP and ABECB	
Macrolide-resistant S. pyogenes	15 isolates worldwide from Phase 3 pharyngitis	
Atypicals; C. pneumoniae, M. pneumoniae, Legionella spp.	15 isolates worldwide per organism (include positive serology) from Phase 3 CAP	



Bulk Drug Manufacturing
Ashok Bhatia



Bulk Drug Manufacturing Agenda

Agenda

- Chemistry
- · Process Strategy and Review
- · Cost Review and Projection

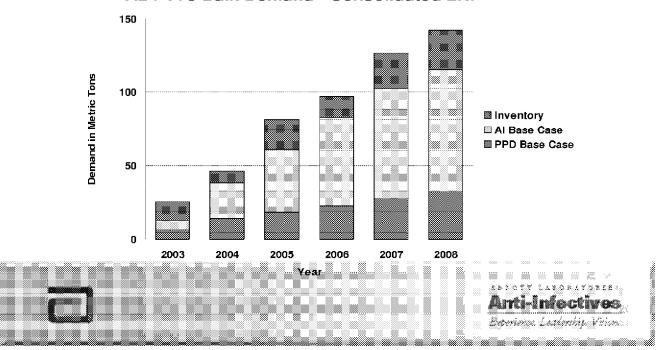


Bulk Drug Manufacturing Macrolide Structures

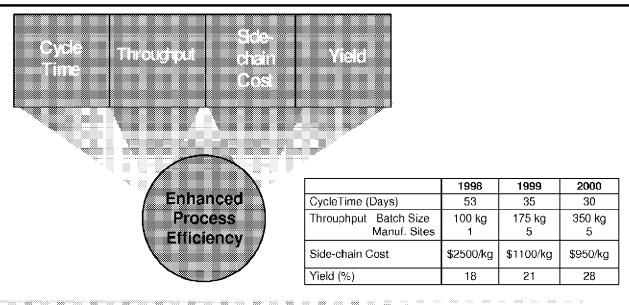
Bulk Drug Manufacturing ABT-773 Synthesis

Bulk Drug Manufacturing Drug Substance Demand

ABT-773 Bulk Demand - Consolidated LRP



Bulk Drug Manufacturing Process Improvements





Bulk Drug Manufacturing Comparison of Projected & Actual Demand/Cost

2001

2000

Bulk Drug	Demand (kg)	1,400	2,520	1,
	Actual (kg)	1,488	2,815	
O = = + /l = =:				

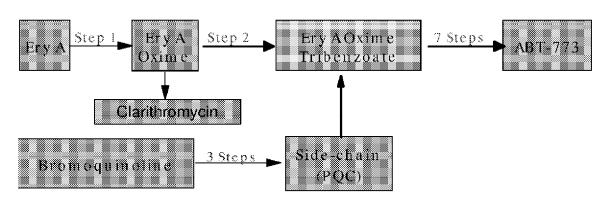
1999

Cost/kg

Demand (kg)	1,400	2,520	1,675
Actual (kg)	1,488	2,815	
Projected (\$)	\$10,000	\$6,500	\$5,000
Actual (\$)	\$7,800	\$5,400 (est.)	



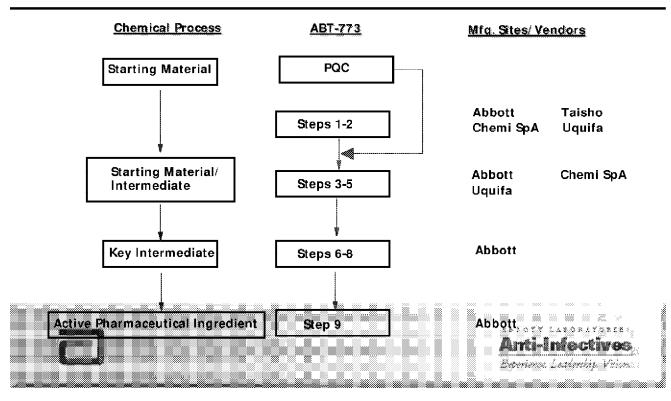
Bulk Drug Manufacturing Synthesis



- · Bromoquinoline sources from India and China
- · Side-chain outsourced from India and Europe
- · Intermediates up to Step 5 outsourced/internal



Bulk Drug ManufacturingManufacturing Strategy: Starting Materials & Intermediates



Bulk Drug Manufacturing Step 5 as Starting Material

Criteria:

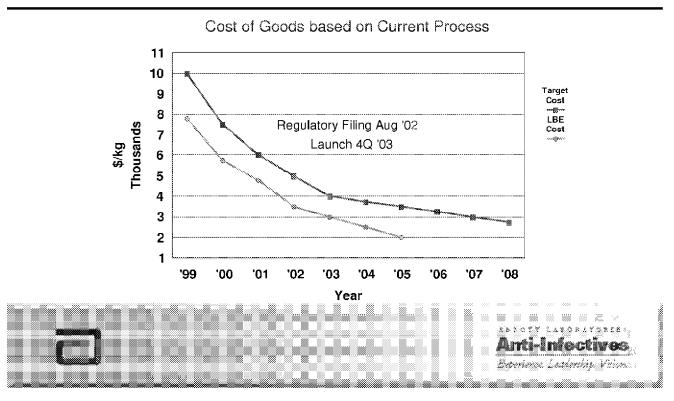
Readily available at commercial scale Structure incorporated in Drug Substance molecule Well-characterized and known impurity profile Prepared by know methods

Advantages:

Commercial flexibility – additional manufacturers Process improvements (changes)without FDA prior approval Cost advantage



Bulk Drug ManufacturingProjected Bulk Drug Costs



Bulk Drug Manufacturing Projected Annual Capacity, Single Site

Bldg C7A/ NC 15MT Bldgs C17 and C7A/ NC 50MT

Alternative strategies:
Step 8 at vendor site(s)
Manufacturing in Abbott, Puerto Rico



Bulk Drug Manufacturing Summary

Summary

- A viable process developed for commercial launch
- · On track to achieve commercial target cost
- · Identified strategies to meet long term bulk substance demand



Tablet Key Issues



QT Prolongation

Dave Morris

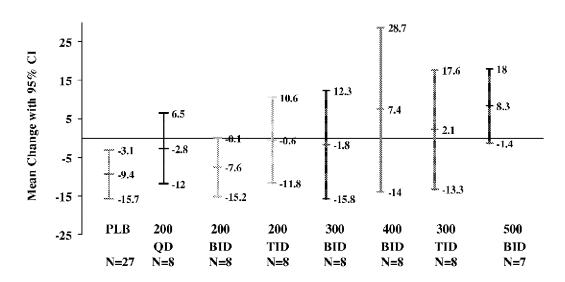


Summary of ECG

- A possible dose effect in Phase I at total daily dose >=800mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole.
- No concentration response in Phase I studies (<=300mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies.
- · Will continue to monitor QT in Phase III programs.



Mean Change of QTC (Multiple Rising Dose Study)



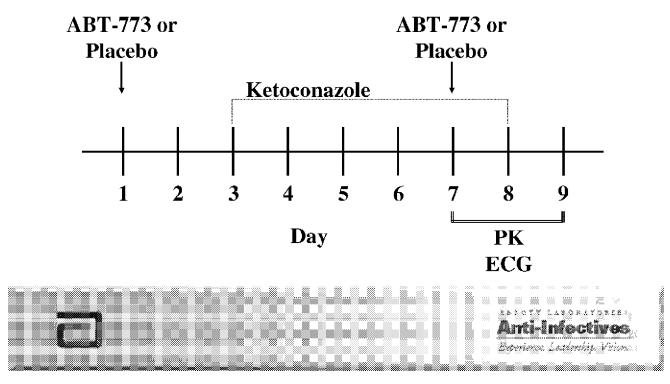


Multiple Rising Dose Study

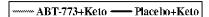
- No subject had QTc increase > 60 msec
- 3 subjects had QTc increase 30-60 msec (>=800mg/day)
- No subject had QTc of >500 msec
- · No syncope observed

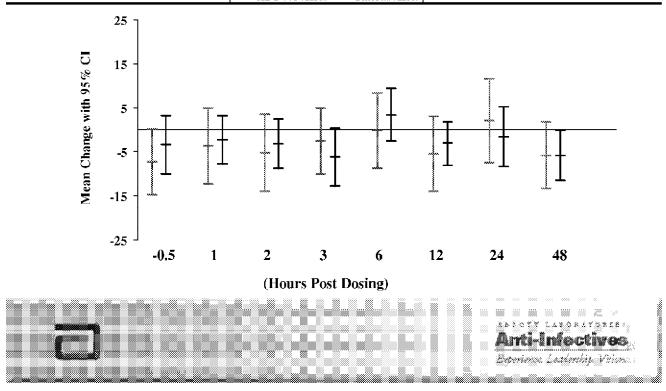


Ketoconazole Interaction Study

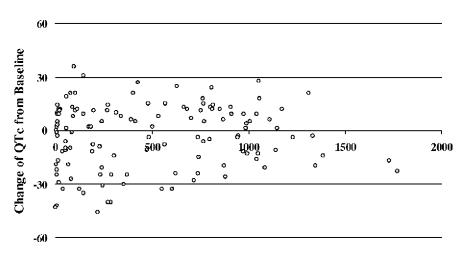


$\label{eq:mean_change} Mean \ Change \ of \ QTC \\ (Ketoconazole \ Interaction \ Study - N = 18)$









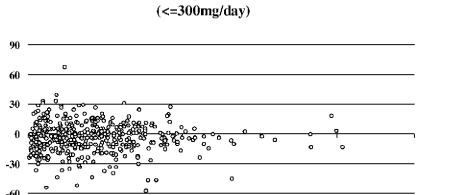
ABT-773 Plasma Concentration



Ketoconazole Interaction Study

- No subject had QTc increase > 60 msec.
- 2 subjects had QTc increase of 30-60 msec.
- No subject had QTc of >500 msec
- · No syncope observed





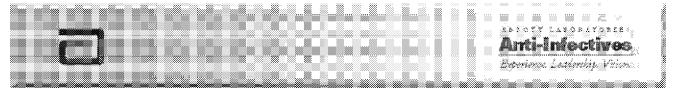
Pooled Multiple Dose Studies

ABT-773 Plasma Concentration

1500

2000

2500



1000

Change of QTc from Baseline

-90 -0

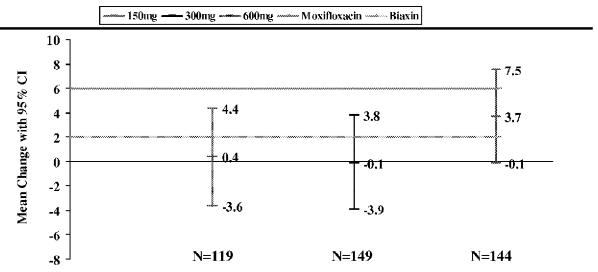
500

All Phase I Studies

- Total of 11 syncopes reported
 - 5 were pre-dosing
 - 6 were post-dosing
- · All associated with blood draw



Mean Change of QTc from Pretreatment to During Treatment (Phase IIB - Based on Cardiologist Reading)





Phase IIA/B

- · 2 syncopes reported
 - 1 was immediately upon first dose on Day 1 (600mg QD)
 - 1 was 7 days post last dose (100mg TID)



Liver Function Dave Morris

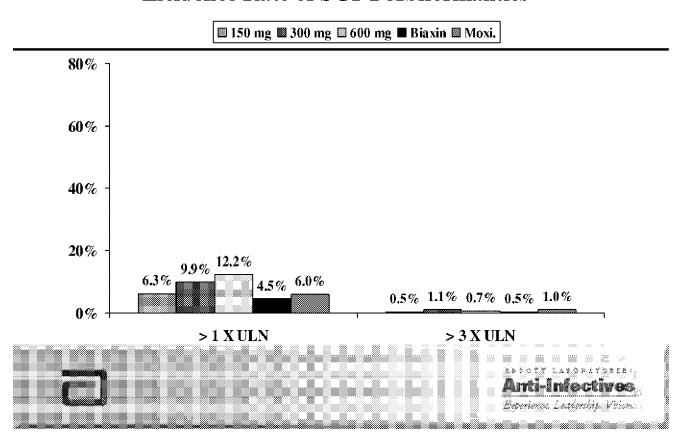


LFT Summary

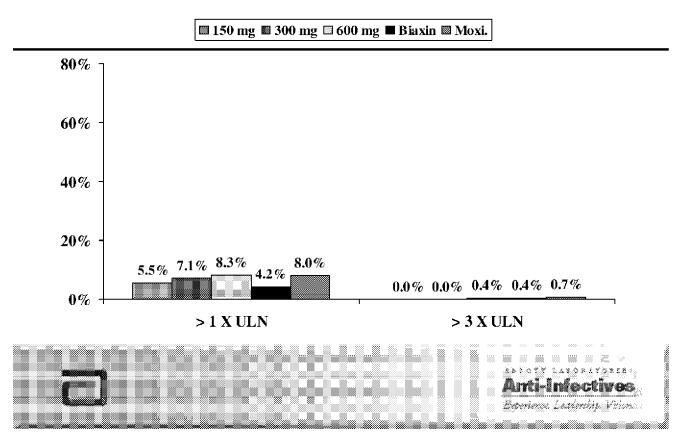
- No evidence of LFT issue in Western subjects.
- · No consistent evidence of dose response.
- · Japanese bridging study results should be confirmed.
- · Will continue to monitor LFT in Phase III programs.



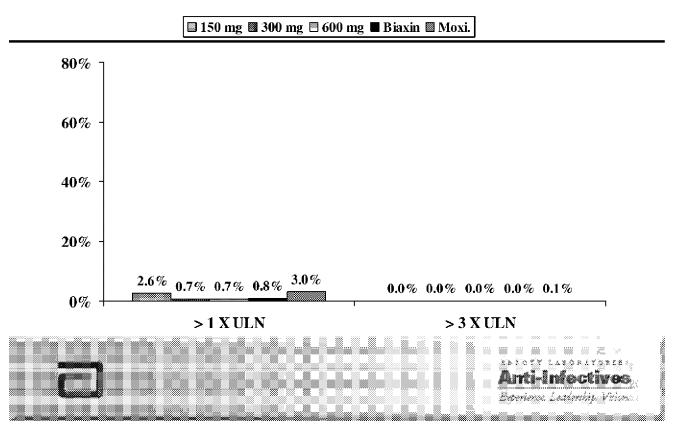
Incidence Rate of SGPT Abnormalities



Incidence Rate of SGOT Abnormalities



Incidence Rate of Bilirubin Abnormalities



Very high LFT Results: Phase II

		SGPT*	SGOT*	GGT\$	Alkaline Phosphatase*	Total Bilirubin&
	150mg QD					
	% (N)	0/181	<1% (1/192)	<1% (1/183)	0/200	0/201
	95% ÚL	2%3%	3%	2%	2%	
	300mg QD					
	% (N)	<1% (2/256)	<1% (1/ 267)	<1% (1/ 2 51)	0/278	0/288
	95% UL	3%2%	2%	1%	1%	
	600mg QD					
	% (N)	<1% (1/256)	<1% (1/263)	0/252	0/273	0/287
	95% ÚL	2%2%	2 %	1%	1%	

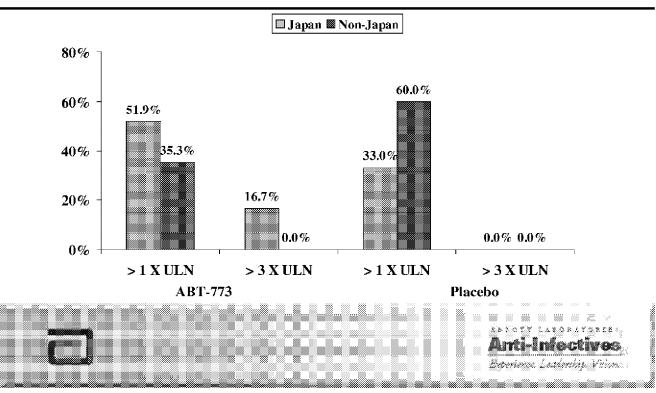
^{*: &}gt;= 3*NUL

[&]amp;>=2 mg/dl.. Note: subject had normal LFT at baseline.

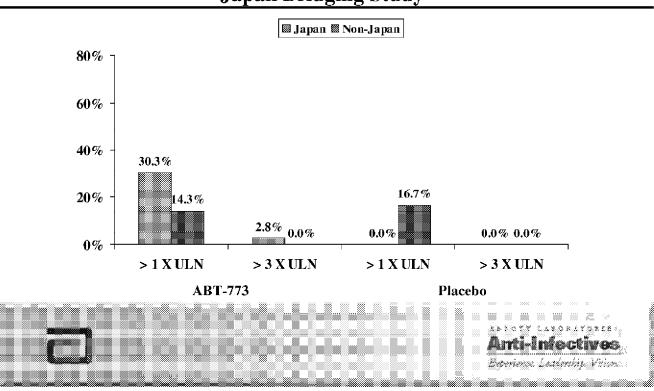


^{\$: &}gt;=5*NUL

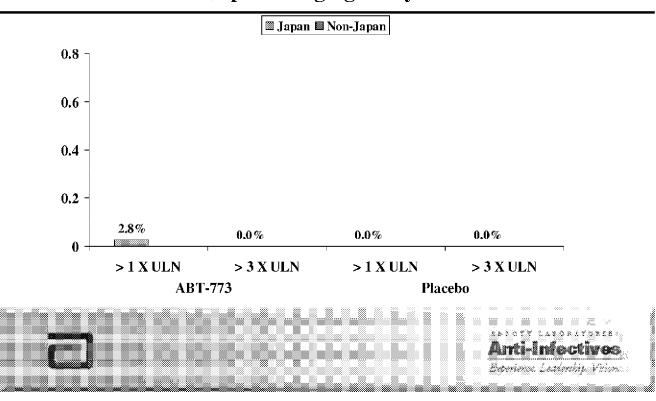
Incidence Rate of SGPT Abnormalities Japan Bridging Study



Incidence Rate of SGOT Abnormalities Japan Bridging Study



Incidence Rate of Bilirubun Abnormalities Japan Bridging Study



PK Profile Linda Gustavson



Regulatory Jeanne Fox

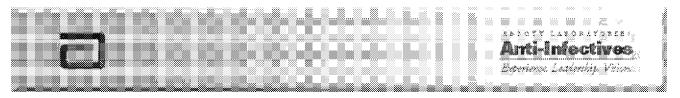


ABT-773 Regulatory Status

- Original U.S. Oral IND submitted 2/2/99
- Phase 3 pivotal trials initiated 11/00
- End-of-Phase 2 Clinical FDA meeting 11/27/00
- End-of-Phase 2 CMC FDA meeting target 1/01
- Tablet NDA submission target 8/02



- ABT-773 Potential for QT Prolongation
 - QT issue is hot button for FDA
 - Question whether ketolides behave like macrolides
 - FDA requested additional dog tox work to evaluate QT
 - Required to include ECG monitoring in pivotal Phase 3 studies
- · ABT-773 Potential for QT Prolongation
 - telithromycin (Ketek) data residing at FDA
 - -Advisory Meeting scheduled for January
- FDA may require a Phase 1 study in patients with underlying cardiac disease
- Some antimicrobials now contain warnings for QT prolongation



- · ABT-773 Potential for Liver Toxicity
 - Ketolides similar to macrolides?
 - Request for additional dog tox work
 - telithromycin (Ketek) data residing at FDA
 - Advisory meeting scheduled for January
- · Plan to conduct routine liver monitoring in all Phase 3 studies



- · Indication to treat resistant pathogens
- FDA skepticism regarding clinical significance of "macrolide-resistant S. pneumo"
- · FDA will require "body of evidence"
 - excellent eradication of susceptible organisms
 - > 10 resistant organisms eradicated to include good proportion of bacteremic CAP patients



Miscellaneous

- Based on NDA timing, potential good candidate for E-submission
- Timing of IV program may affect ability to document effectiveness vs. resistant pathogens in bacteremic patients
- Timing of pediatric program and "due diligence" for formulation development critical



Commercial Profile, Positioning & Financials Rod Mittag



I.V. Program Carol Meyer



ABT-773 IV Program Formulation Objectives

- Reconstituted solution . Once a day dosing. Low pain on injection
- Lyophilized powder, consisting of ABT-773 and a counterion base.
- One strength, in a flip-top vial and the ADD Vantage system at launch.
- Diluent volume 100ML, with length of infusion (30 to 60 minutes) and type of diluent (Dextrose 5% and/or normal saline) <u>TBD</u> based on animal pain models, clinical and stability studies.



ABT-773 IV Formulation Status

- PPD funded Program 01/00-08/00 (\$1.4MM)
 - Formulation development (lactate salt,lyophilized powder)
 - Animal pain models
 - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 (\$0.8MM)
 - Two week Tox study (rat)
 - Clinical supplies for Phase I
 - Stability program



ABT-773 IV Formulation Animal Pain Study Results

- Assessed 6 prototypes(3 different counterions at 2 pH levels) vs clarithromycin IV and azithromycin IV
- Animal pain models showed no differentiation among all three compounds
- · Results not conclusive
- Chose ABT-773 lactate as the prototype to test in Phase I studies based on manufacturability and stability.

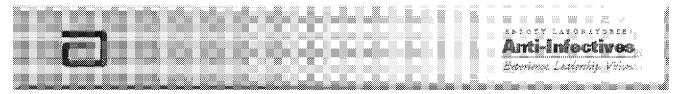


EXHIBIT 608 Part 9

ABT-773 IV Planned Clinical Program

Mar/01

June/01

Oct/01

· Single Dose -rising Phase I study

· Multiple Dose Phase I with selected dose

· Initiate Phase III

2 step-down CAP studies (US/Europe)

- 2-3 days dosing

- Two seasons to complete

 Filing Aug/03



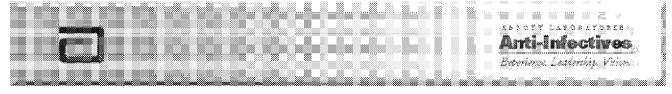
ABT 773 IV Program Summary

Comments

- Funding for '01 not available with PPD/HPD
- Go/No go could be made after Phase I based on safety profile(pain,QT,GI)
- Milestone funding recommended (\$MM)
- Assuming Go, '01 budget estimated \$7MM
- IV will help to obtain resistant S. pneumo claim



Pediatric Program Carol Meyer



ABT-773 Pediatric Program Formulation Objectives

· Develop coated particle formulae for global use

- Formulate coated particles for Suspension 150mg/5mL & 300mg/5mL
- Formulate coated particles as a dry syrup, sprinkle or sachet.

Desired Properties

- Once a Day Dosing
- Acceptable 'Initial Taste'
- Minimal 'After Taste'
- No Unpleasant Mouth-feel
- Acceptable Color and Flavor
- No Refrigeration Required.



ABT-773 Pediatric Program Status

- Initiated January 2000
- 2000 Funding through first PK study milestone only (\$MM)

Prototype Development completed (granules for suspension)
 Phase I Single Dose Study - 2 prototypes completed
 First set of Taste Evaluations completed
 Comparative Taste vs Clari and Azi

May '00
Aug '00
Sep/00
Dec/00



ABT-773 Pediatric Program Formulation Trade-off

ABT-773 Pediatric - Reconstitutable Suspension





ABT 773 Pediatric Program Challenges

- Pharmacokinetic Profile (plasma, middle ear fluid)
- Taste
 - Masking Bitter Taste
 - Flavor
 - Mouth-Feel
- Preserving the Reconstituted Suspension
- Ease of Manufacture
- Cost



ABT 773 Pediatric Program Formulation Development

· Formula Selected

- Zein Coated Stearine 07 Based Particles
- Formula acceptable both from an Organoleptic and Dog Bioavailability standpoint
- Two prototypes
 - · Same core
 - Different coating levels (15% and 25% coating)



Taste Assessment

- · Taste Assessment conducted by Arthur D Little
 - Utilized a Flavor Profile Method of Sensory Analysis
- Task 1: Sensory Analysis of Aqueous Solutions/ Suspensions of Uncoated Drug Substances
 - ABT-773
 - Clarithromycin (Biaxin®)
 - Azithromycin (Zithromax®)
- Task 2: Sensory Analysis of Coated ABT-773 Prototypes



Taste Assessment

Sensory Analysis of Uncoated Drugs Summary of Results

The three drug substances can be ranked from most to least bitter as follows:

Drug Substance	Concentration (ppm) Which Exhibits an Initial Bitter Intensity ≤1 (Slight)
ABT-773	0.79
Clarithromycin	4.2
Azithromycin	15

• ABT-773 is approximately five times more bitter than clarithromycin



Taste Assessment

- The flavor quality of the two coated drug prototypes was similar—the bitter intensity was moderate-to-strong initially and throughout the aftertaste.
 - The observed bitter intensity is well above the "consumer concern level" of a slight intensity.
 - We believe that the lingering bitterness results from the "sustained release" of drug from the coated drug particles that lodge in the oral cavity (both prototypes exhibited a moderate amount of grittiness).



ABT 773 Pediatric Program Phase I PK Results

• The AUC ratio (suspension:tablet) is 75% and the Cmax ratio is 77 to 79% for the two suspension formulations (SC-1a and SC-1b) respectively.

Document 362-11

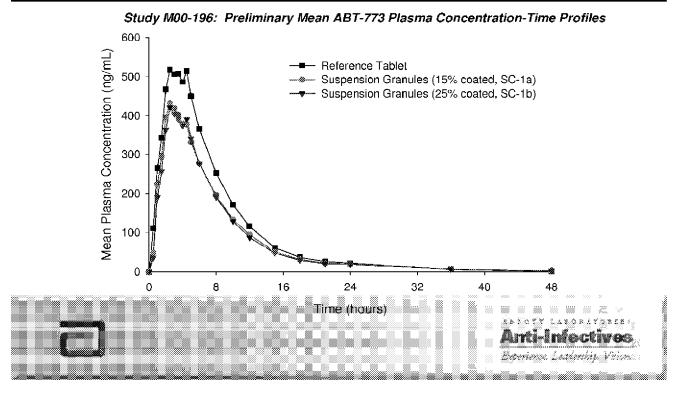
Pharmacokinetic Parameters	Tablet (N = 42)	Suspension (SC-1a) (N = 41)	Suspension (SC-1b) (N = 41)
Tmax (h)	3.0 ± 1.3	2.6 ± 1.0	2.8 ± 1.0
Cmax (ng/mL)	628 ± 263	505 ± 234	494 ± 223
AUC_{∞} (ng•h/mL)	4527 ± 1830	3645 ± 2226	3521 ± 1868
t½ (h)‡	6.3	6.8	6.7
Cmax Ratio (test/ref)*		0.79	0.77
AUC $_{\infty}$ Ratio (test/ref)*		0.75	0.75

[‡] Harmonic mean.

^{*} Geometric mean



ABT 773 Pediatric Program Phase I PK Results



ABT 773 Pediatric Program Proposed Clinical Program

Proposed Pediatric Clinical Studies for Registration (Phase 1, 2, 3)						
Indications/Type Phase Studies Subjects						
PK adult single rising dose, multiple rising dose/effect of food	1a 1b	4	96			
Otitis Media (dose ranging), PK in children	2	1	100			
Otitis Media, Pharyngitis, CAP	3	6	1800			



Proposed Clinical Program

· First option

- Develop a pro-drug with no immediate after taste, stable in a suspension formulation, hydrolized in acidic pH and absorbed as parent drug.
- Three pro-drugs under study (benzoyl,TMB,ES)

Second option

- Continue improving after taste, PK of parent drug formulation.
- Recommend first option with Go/No go in 06/01 (\$MM)



Japan Program Carol Meyer



Japan Program

- Japan development is planned in coordination with Taisho and Dainabot
- · Meetings are held at least 3 times a year to review developments
- Taisho funds 10.69% of global development costs and 50% of local Japan costs.
- Bridging strategy is primary plan for development in Japan
- Findings in first PK trial in Hawaii resulted in repeat of Phase I in Japan



Japan Program Phase I Findings

- · Initial Phase I study conducted in Hawaii with Japanese and non-Japanese subjects
- Results indicate 50% higher AUC and Cmax in Japanese vs non-Japanese
- · Liver enzyme elevations were noted in a few Japanese subjects, however it was not dose related
- · Decision made to repeat Phase I in Japan



Japan Program Clinical Plan

Phase I in Japan
 Food Effect Study
 Nov/00

Single and multiple dose study
 Dec/00

Review data (Abbott/Taisho)April/01

• PK data Japanese vs Caucasian

· Development program strategy

- Present Kiko data and recommend development program May/01

Start Tissue Conc. Study2Q/01



Japan Program Clinical Plan

- PK similar in Japanese and Caucasians (12/02 filing)
- · Recommend to Kiko same dose in Japan as in ex-Japan
 - Recommend to Kiko one comparative bridging study in CAP (Phase III) and several smaller local studies in SSS, Dentistry,Otolaryngology,UTI and pan- bronchiolytis
 - Taisho agreement necessary prior to Kiko meeting
- PK different in Japanese and Caucasians(12/03 filing)
 - Phase II dose ranging study in CAP (Bridging study)
 - - Phase III comparative study will be required
 - Full development time line
 - Implications on Taisho cost-sharing



Summary Carl Craft



Backups

Competitive Update, Ketek-Rod Mittag
OS/IV/overall financials-Rod Mittag



IV/OS/Overall Financials

Rod Mittag



FDA Contact Report

Compound/Product Discussed: ABT-773 - End of Phase 2 Meeting

Application Type & Number: IND 57,836 Date of Contact: November 27, 2000

	Name & Title	Group
FDA Person(s) Contacted	Jose Cintron, Sr. Project Mgr	Anti Infective Division
	Mercedes Albuerne, Medical Team Leader	и
	Nasim Moledina, Medical Officer	и
	Mamodikoe Makhene, Medical Officer	и
	Alma Davidson, Medical Officer	н
	Daphne Lin, Statistics Team Leader	и
	Erica Brittain, M.D., Statistics Reviewer	и
	Terry Peters, Pharm/Tox Reviewer	и
	Robert Osterberg, Pharm/Tox Team Leader	н
	Lilian Gavrilovich, Deputy Director	н
	Charles Bonapace, Biopharm Reviewer	и
	Frank Pelsor, Biopharm Team Leader	и
	Sousan Altaie, Micro Reviewer	н
	Jean Mulinde, Medical Officer	PT .
	Jim Timper, Chemistry Reviewer	rr .
	Charles Cooper, Medical Officer	н
	Albert Sheldon, Micro Team Leader	п
	Janice Soreth, Acting Division Director	и
	John Alexander, Medical Officer	п
	Diane Murphy, Office Director	Office of Drug Evaluation - IV
Abbott Representative(s)	Greg Bosco, Sr. Product Mgr	Regulatory Affairs
•	Jeanne Fox, Director	Regulatory Affairs
	Jie Zhang, Statistician	Clinical Statistics
	Joaquin Valdes, Physician	Anti Infective Venture
	Carol Meyer, Operations Manager	Anti Infective Venture
	Bob Flamm, Microbiologist	Microbiology
	Linda Gustavson, Pharmacokineticist	Clinical Pharmacokinetics
	David Morris, Statistician	Clinical Statistics
	Maria Paris, Physician	Anti Infective Venture
	George Aynilian, Associate Venture Head	Anti Infective Venture
	Carl Craft, Venture Head	Anti Infective Venture
	John Leonard, Vice President	Research & Development
	Reid Patterson, Vice President	Drug Safety

 $\underline{\textbf{Subject of Meeting}};$ The purpose of the meeting was to introduce the oral tablet Phase 3 development plan, discuss potential issues, and address any questions regarding the plan or Phase 2 study results.

Report of Meeting:The meeting began with introductions from both sides. As Carl began his presentation, Dr. Soreth stated that in case there was some misconception regarding the result of the telecon held on 11/20/00, she wanted to say that the ABT-773 program was at this point not on clinical hold.

Carl began his presentation with a slide showing the proposed indications and treatment durations we were planning to file in the NDA. He showed a series of slides which summarized all the Phase 3 studies we are planning; those starting in 2000 and those slated for 2001. This was the first time FDA saw the proposed dose-selection studies for pneumonia (CAP) and sinusitis (ABS). Dr. Brittain had a few questions regarding the objectives of the studies and the proposed interim analyses, but stated that she would be faxing us all of her comments in more detail. Carl stated that the objectives of the studies were: to pick a dose for the large, well-controlled, comparative, pivotal studies to be conducted in 2001, and to meet the specific pathogen criteria as required for the second supportive trials in the FDA guidance for CAP and ABS. There was lengthy discussion around these study designs. It was stressed to FDA that we still intend to conduct a large, well-controlled, double-blind, comparative trial for each of these indications. FDA advised us there might be a problem using Augmentin 875 mg BID for the sinusitis trial. They would prefer us to use 500 mg TID. Carl committed that we would provide the results from these two trials to FDA for review.

The next slide shown detailed our intention to request a claim for macrolide and penicillin resistant bacteria and atypical bacteria, and the supporting data we proposed to provide to support these claims. Dr. Albuerne stated that we could pool isolates for CAP and ABECB but not for ABS (we proposed pooling from all three). Dr. Soreth stated that there is currently no guidance document available addressing specific requirements for resistant claims but mentioned that there is data from other products (e.g. levofloxacin) that is available in the public domain. As far as our proposal for number of isolates, numbers >10 would be acceptable with good data for susceptible pathogens, but there has been an instance (with linezolid) where <10 was not approvable, but in that case only one or two patients had bacteremia and responded well to therapy. It was stated that a number of bacteremic patients would be required in order to adequately evaluate clinical success against penicillin resistant Strep pneumoniae. The comment was made that with oral therapy alone we would probably be hard pressed to find enough patients with hacteremia, that oral/IV therapy gave us a better chance. Dr. Soreth stated that FDA has not seen data supporting "macrolide resistant Strep pneumoniae" as a clinical concern. They also said that there is no good body of evidence supporting macrolide resistant Strep pyogenes either.

The next topic discussed was the ECG monitoring plan regarding the six Phase 3 studies starting in 2000. We proposed that ECG's would be performed in 5/6 of the studies. In total, we would be gathering ECG data on ~2000 subjects exposed to ABT-773. ECGs will be performed pre-, during, and post-therapy. Additionally, the timing of the ECG and the timing of the dose before the ECG will be documented. FDA requested that we amend all informed consents to mention possible effects on cardiac repolarization caused by ABT-773. Various examples of wording was then discussed and we agreed that we would amend the informed consents for all IND studies. Dr. Soreth asked why we were not doing ECG's in the sixth study. Carl stated that the European pharyngitis study would not include ECG's based on recommendations of our European advisors based on the number of existing visits and the likelihood of subject reluctance to participate in a trial for this disease with so many visits. FDA strongly disagreed with this justification. Dr. Murphy expressed concern that we were blatantly misinforming the subjects in that trial by not including a procedure that would monitor a potentially serious adverse event that was being included in all other studies. This issue was left unresolved. Other comments regarding the collection of a blood sample taken at the on-therapy ECG, etc. were made. All issues were addressed in a subsequent written correspondence by FDA (faxed 12/5/00, Abbott response 12/14/00).

Relating to the topic of possible adverse effects on cardiac repolarization, the results of the previously submitted toxicology studies were discussed. Dr. Peters requested additional data in the dog model. The requested study should be a two-week acute study with telemetry and the study can run concurrent with the Phase 3 clinical trials. At this point Reid offered to provide some background information. He indicated that the emetic activity of ABT-773 in the unanesthetized dog limits exposure in this species, leading to our selection of the cynomolgus monkey as the non-rodent model. While the primate did not indicate a risk for QTc prolongation, exposures of 17 times the human Cmax in anesthetized dogs did lead to some prolongation. Owing to differences in protein binding, the dog receives about 3 times the amount of unbound drug than does the human with identical exposures, perhaps expanding our margin of safety. Various proposals for the study were discussed between Reid and Drs. Peters and Osterberg. We committed to sending draft protocols to Dr. Peters for review.

Carl briefly discussed the Phase 2 ECG data. Dr. Soreth informed us that they have begun to ask for special population studies with drugs that show an effect on ECG's. In this case they would be looking at a study in otherwise healthy subjects with underlying cardiovascular disease. She commented that only looking at the effects

of ABT-773 in comparator trials might not be realistic (i.e., cisapride and terfenadine looked safe in the clinic too). Dr. Murphy commented that it is in both of our best interests to get all the information we can to show how to use the drug safely.

The rest of the meeting was spent answering specific questions regarding the four main Phase 3 trials (CAP, ABS, ABECB & pharyngitis). Most of the comments related to minor protocol changes. All of the issues discussed were subsequently provided to Abbott by fax on 12/5/00. Abbott formally responded to the fax in IND 57,836, Serial No. 066, dated 12/14/00.

Action Items:

- Amend Phase 3 informed consents to incorporate statements relating to: possible effects on cardiac repolarization caused by ABT-773, possible interactions with other drugs, and stronger precautions for women of childbearing potential.
- Provide full narratives from Phase 2 studies of all patients who had an adverse event of syncope or elevated liver enzymes.
- Submit draft toxicology protocol(s) for comment prior to initiating the studies.
- · Submit results from CAP and ABS dose-selection trials when available.
- Submit draft protocols for the two well-controlled, comparative, pivotal studies for CAP and ABS (to be conducted in 2001) for comment as soon as available.

AGENDA

Introductions

Proposed Indications and Treatment Duration

Phase 3 Studies

Plan for CAP and Sinusitis Dose-Selection Studies

Plan for Resistant Pathogens Claim

ECG Monitoring Plan for Phase 3

Resolution of Clinical Hold

ABT-773 Proposed Indications and Treatment Duration

	Dosage	Duration	
Infection	(QD)	(days)	
Pharyngitis/Tonsillitis due to			
S. pyogenes*	150 mg	5	
Acute bacterial sinusitis due to			
H . $influenzae$	150 mg (or BID)	10	
M. $catarrhalis$	150 mg (or BID)	1.0	
S. pneumoniae**	150 mg (or BID)	1 ()	
Acute bacterial exacerbation			
of chronic bronchitis due to			
H. influenzae	150 mg	5	
H . $parainfluenzae$	150 mg	5 5 5	
M. catarrhalis	150 mg	5	
S. pneumoniae**	150 mg	5	
Community-acquired			
pneumonia due to			
C. pneumoniae	150 mg (or BID)	10	
H. influenzae	150 mg (or BID)	10	
$L.\ p$ n e u m o p h i l a	150 mg (or B ID)	10	
M. pneumoniae	150 mg (or BID)	10	
S. pneumoniae**	150 mg (or BID)	10	

Including macrolide-resistant strains.
Including penicillin-resistant and macrolide-resistant strains.

Phase 3 Studies

Studies starting in year 2000:

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Test of Cure	Location
M00-223	Pharyngitis	150 mg QD 5 days	Penicillin V 500 mg TID	260	Days 17-20 (12-15 days after last dose)	US (IND)
M00-222	Pharyngitis	150 mg QD 5 days	Penicillin V 500 mg TID	260	Days 16-18 (11-13 days after last dose)	EU (Non-IND)
M00-216	ABECB	150 mg QD 5 days	Azithromycin	300	Days 14-19 (9-14 days after last dose)	US, Canada IND
M00-217	ABECB	150 mg QD 5 days	Levofloxacin	250	Days 14-19 (9-14 days after last dose)	EU (Non-IND)

Phase 3 Studies

Studies starting in year 2000 (Cont.):

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Test of Cure	Location
M00-225	Sinusitis	150 mg QD vs.	None	600	Days 19-24 (9-14 days after	US, EU (IND)
		150 mg BID 10 days			last dose)	
M00-219	CAP	150 mg QD vs. 150 mg BID	None	800	Days 19-24 (9-14 days after last dose)	US, Canada, EU (IND)
		10 days			,	

Phase 3 Studies

Studies starting in year 2001:

Study	Indication	Comparator	Number ABT-773 Subjects	Test of Cure	Location
M00-221	CAP	Levofloxacin	225	Days 19-24 (9-14 days after last dose)	US, Canada (IND)
M00-220	CAP	Augmentin or Amoxicillin	250	Days 19-24 (9-14 days after last dose)	EU (Non-IND)
M00-226	Sinusitis	Augmentin	225	Days 19-24 (9-14 days after last dose)	US, Canada (IND)
M00-218	Sinusitis	Augmentin or Quinolone	250	Days 19-24 (9-14 days after last dose)	EU (Non-IND)

Objectives of Dose-Selection Studies for CAP and Acute Bacterial Sinusitis

- Establish dose for Phase 3 pivotal trials
- Satisfy FDA recommendations for open studies to provide a minimum number of evaluable subjects with confirmed microbiologic etiology

ABT-773 Dose-Selection Study for CAP - M00-219

- 800 treated subjects will provide at least 80% power to detect a 10% difference in cure rates for clinically and bacteriologically evaluable subjects.
- At least 80 clinically and bacteriologically evaluable subjects will be studied at the dose chosen for pivotal trials (FDA Guidance).
- Investigators and subjects will be blinded. Efficacy and safety will be monitored by the sponsor.
- The study may be stopped once a dose is chosen and minimum requirements are met.

Initial Stopping Rule M00-219

- At N=200, choose dose that has
 - Statistically significantly better cure rate at p-value < 0.001
 - Better eradication rates for *S. pneumoniae* and *H. influenzae*
 - Acceptable safety profile
- Provide results to FDA for review

Subsequent Stopping Rule for Superiority -M00-219

- At N=400 to 800, choose dose that has
 - Statistically significantly better cure rate p-value < 0.025 before full enrollment p-value < 0.050 at full enrollment
 - Better eradication rates for S. pneumoniae and H. influenzae
 - Acceptable safety profile
- Provide results to FDA for review

ABBT205268 Confidential

Subsequent Stopping Rule for Equivalence - M00-219

- At N=400 to 800, choose lower dose if
 - Lower bound of two-sided 95% CI for the difference between doses (150 mg QD - 150 mg BID) in cure rates greater than -10%
 - Similar eradication rates for S. pneumoniae and H. influenzae
 - Acceptable safety profile
- Provide results to FDA for review

ABT-773 Dose-Selection Study for ABS - M00-225

- 600 treated subjects will provide at least 80% power to detect 10% difference in cure rates for clinically evaluable subjects.
- For the dose chosen for pivotal trials, acceptable microbial and clinical outcome in 25 patients with *H. influenzae*, 25 patients with *S. pneumoniae*, and 15 patients with *M. catarrhalis* will be established (FDA Guidance).
- Investigators and subjects will be blinded. Efficacy and safety will be monitored by the sponsor.
- The study may be stopped once a dose is chosen and minimum requirements are met.

Initial Stopping Rule M00-225

- At N=200, choose dose that has
 - Statistically significantly better cure rate at p-value < 0.001
 - Better eradication rates for *S. pneumoniae* and *H. influenzae*
 - Acceptable safety profile
- Provide results to FDA for review

Subsequent Stopping Rule for Superiority -M00-225

- At N=400 to 600, choose dose that has
 - Statistically significantly better cure rate p-value < 0.025 before full enrollment p-value < 0.050 at full enrollment
 - Better eradication rates for S. pneumoniae and H. influenzae
 - Acceptable safety profile
- Provide results to FDA for review

ABBT205272 Confidential

Subsequent Stopping Rule for Equivalence - M00-225

- At N=400 to 600, choose lower dose if
 - Lower bound of two-sided 95% CI for the difference between doses (150 mg QD - 150 mg BID) in cure rates greater than -10%
 - Similar eradication rates for S. pneumoniae and H. influenzae
 - Acceptable safety profile
- Provide results to FDA for review

Proposed Claim for Macrolide or Penicillin Resistant Bacteria and Atypicals

Claim	Supporting Data
Macrolide-resistant S. pneumoniae	15 isolates worldwide from Phase 3 - CAP, ABECB, and ABS
Penicillin-resistant S. pneumoniae	15 isolates worldwide from Phase 3 - CAP, ABECB, and ABS
Macrolide-resistant S. pyogenes	15 isolates worldwide from Phase 3 - Pharyngitis
Atypicals; C. pneumoniae, M. pneumoniae, Legionella spp.	15 isolates worldwide per organism (include positive by serology and positive by serology + PCR) from Phase 3 - CAP

ECG Monitoring Plan

- Six Phase 3 studies starting Nov/2000
- ECGs will be performed in 5/6 studies
 - Acute bacterial exacerbation of chronic bronchitis (two studies)
 - Community-acquired pneumonia
 - Pharyngitis
 - Acute bacterial sinusitis
- ~ 2000 subjects exposed to ABT-773

ECG Monitoring Plan (Cont.)

- ECGs will be performed:
 - Pre-Therapy
 - During Therapy
 - Evaluation 2 (Days 3-5)
 - Post-Therapy
 - Evaluation 3 (24-72 hours after last dose) or
 - Evaluation 4 (12-15 days after last dose)
- Additional Information collected:
 - Timing of ECG
 - Timing of dose before ECG

ECG Monitoring Plan (Cont.)

Centralized Method:

- Covance Central Diagnostics
- 12-lead MTX 2
- Bazett's formula will be used for initial reading by Covance
- Other QT corrections will be performed later
- Single cardiologist to interpret all ECGs

Confidential ABBT205277

Support for Conduct of Phase 3 Clinical Program

Preclinical

- Extensive PK & metabolism data to select most appropriate non-rodent species
- 1 month rat study
- 1 month monkey study
- QT purkinje fiber studies
- 3 month rat study
- 3 month monkey study
- QT evaluation in dog underway QT prolongation at 17x therapeutic concentrations

ABBT205278 Confidential

Support for Conduct of Phase 3 Clinical Program

Clinical

- Hepatic Function Results in Phase 1 & 2 ($n \sim 1700$)
 - less than 1% asymptomatic elevation of LFT's from normal to >3 ULN
- QT Results in Phase 1 & 2 ($n \sim 900$)
 - No significant QT prolongation in clinical studies at therapeutic doses below 800 mg/day
- Phase 3 Studies
 - Lower doses than in Phase 2 (maximum dose 300 mg/day)
 - Liver monitoring and QT monitoring included

ABBT205279 Confidential

EXHIBIT 614 Part 1

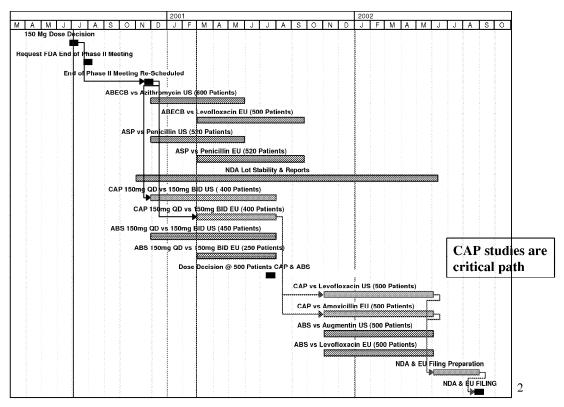
ABT 773 Agenda

- Product Profile impacted by:
 - Ketek FDA advisory
 - New Efficacy data
 - New Safety data
- Summary
 - Narrowing of therapeutic window
 - Increase widening of the CI for the probability of success
 - Reducing NPV of the product
- Future options

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ABT 773 Development Timeline as of March 2001



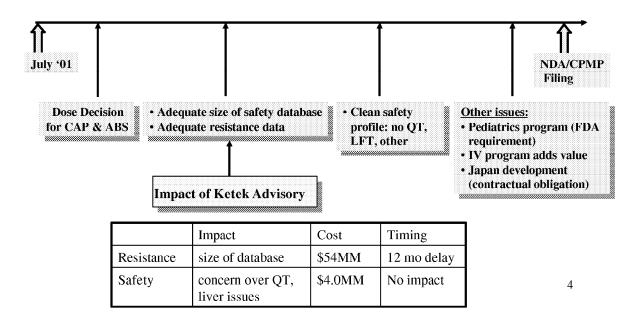
ABT 773 Target Profile

Target Indications				
ABECB 5D QD				
ASP	5D	QD		
CAP	10D	QD/BID		
ABS	10D	QD/BID		

Attribute	ABT 773	Clari	Levo	Azi	Ketek
QD dosing	ABECB/ASP QD CAP/ABS QD/BID	QD	QD	QD No ABS	QD No ASP US
Short-course therapy	ABECB/ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
Efficacy with resistant organisms	Pursuing 15 isolates	Under exploration	Claim for pen-R Strep pneumo (15/15 isolates)	None	Not obtained, pen-R and mac-R (14/17 isolates)
Safety	QT, liver	Approved	Approved	Approved	Large database condition for approval US, EU approval

Filing date dependant on timing of Dose decision and Program size.

Program dependant on technical and regulatory hurdles



Impact of Ketek FDA Advisory

Attribute	ABT 773	Clari	Levo	Azi	Ketek
QD dosing	ABECB/ASP QD CAP/ABS QD/BID	QD	QD	QD No ABS	QD No ASP US
Short-course therapy	ABECB/ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
Efficacy with resistant organisms	Pursuing 15 isolates Increased to 25 isolates	Under exploration	Claim for pen-R Strep pneumo (15/15 isolates)	None	Not obtained, pen-R and mac-R (14/17 isolates)
Safety	QT, liver Added 1000 patients	Approved	Approved	Approved	Large database condition for approval US, EU approval

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Impact of Dose Decision

Attribute	ABT 773	Clari	Levo	Azi	Ketek
QD dosing	ABECB/ASP QD CAP/ABS BID	QD	QD	QD No ABS	QD No ASP US
Short-course therapy	ABECB/ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
Efficacy with resistant organisms	Pursuing 15 isolates Increased to 25 isolates	Under exploration	Claim for pen-R Strep pneumo (15/15 isolates)	None	Not obtained, pen-R and mac-R (14/17 isolates)
Safety	QT, liver Added 1000 patients	Approved	Approved	Approved	Large database condition for approval US, EU approval

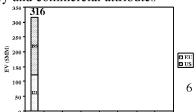
•Assessed six alternative strategies based on technical, regulatory and commercial attributes

•Chose BID dose pending results of ABS and CAP studies

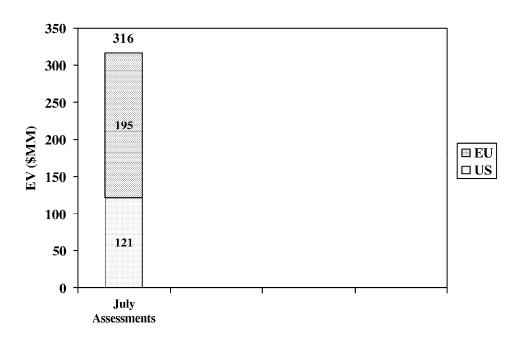
•Start pivotal studies in 2001 winter season

•PK/PD parameters

•Statistical probability of success in comparator studies



ABT 773 Expected Value based on Ketek and Dose decision



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ABT-773 Phase III Clinical Plan (Pivotal Trials)

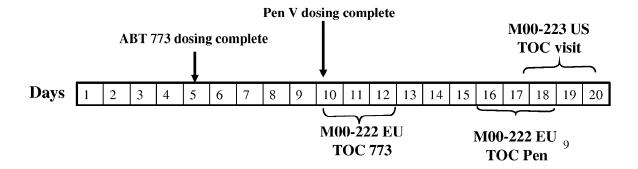
Study	Indication	Comparator	Number ABT-773 Subjects	ABT-773 Dose/ Duration in Days	Status
US, EU (IND) M00-225	Sinusitis	NA	660	150 BID x 10 d 150 QD x 10 d	84-86% interim analysis
US, Canada (IND)	Sinusitis	Augmentin	660	150 BID x 10 d	Await FDA
EU (Non-IND)	Sinusitis	Quinolone	660	150 BID x 10 d	Ready to dose
US (IND) M00-219	CAP	NA	600-800	150 BID x 10 d 150 QD x 10 d	585/600 Unblind Jan
US (IND)	САР	Levofloxacin	660	150 BID x 10 d	Await FDA
EU (Non-IND)	CAP	Amoxicillin	660	150 BID x 10 d	Ready to dose
US	Pharyngitis	Penicillin	520	150 QD x 5 d	Failed
EU	Pharyngitis	Penicillin	520	150 QD x 5 d	209/520
US	ABECB	Azithromycin	600	150 QD x 5 d	578/600
EU	ABECB	Levofloxacin	500	150 QD x 5 d	327/500

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US: M00-223 (IND study)

ABT-773 150 mg QD VS Penicillin V 500 mg TID Streptococcal Pharyngitis/Tonsillitis

- Treatment groups:
 - ABT-773 150 mg on Study Days 1-5
 - Penicillin V 500 mg (250 mg x 2) TID tablets on Study Days 1-10
- 2 different protocol designs for Test-of-Cure (TOC) Visits EU vs US



M00-223 US Pharyngitis Study Eradication Rate at Test-of-Cure Visit

	ABT-773	Penicillin	95% CI	P-value
Bacte	eriological			
PP	74%	90%	(-23.7, -8.0)	< 0.001
	(140/189)	(170/189)		
ITT	64%	81%	(-25.1, -8.0)	< 0.001
	(141/220)	(171/212)		
<u>Clini</u>	cal			
PP	85%	93%		
	(160/188)	(175/188)		

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Pharyngitis and earlier Sinusitis Data are Consistent

- Pharyngitis indication: test of cure is bacteriological Sinusitis cure rates 86% BID vs 84% QD based on clinical cure with presumed eradication.
- Indications at different doses;
 - Sinusitis 150 mg QD less effective than 150 mg BID even at 10 days
 - Pharyngitis result findings consistent with clari failure at 5 days and success at 10 days therapy
- Sinusitis had no comparator and will still be tested

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Impact of Pharyngitis Results on Bronchitis Indication at 150mg QD

- Bronchitis trial likely to succeed based on clinical cure rate (blinded clinical rate 82%)
 - Placebo effect
 - Enriched population FEV1 and FEV1/FVC
- Bacteriological failure in pharyngitis raises issues of bacteriological efficacy at 150mg QD dose
 - S. pyogenes and S. pneumoniae have similar MIC profiles
 - H. influenzae in bronchitis is an important pathogen
- Bronchitis is only indication left at 150mg QD dose
 - will not be supported by CAP data (occult CAP a clinical concern)
- EU approach to bronchitis

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Impact of Dose Decision

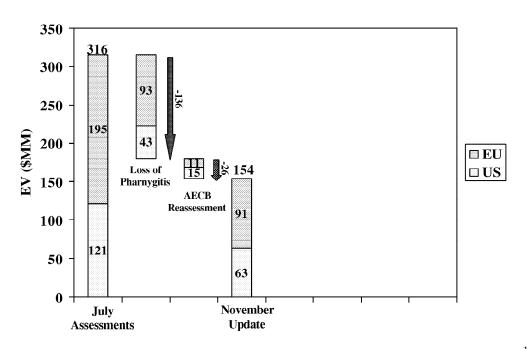
Attribute	ABT 773	Clari	Levo	Azi	Ketek
QD dosing	ABECB/ASP QD CAP/ABS BID	QD	QD	QD No ABS	QD No ASP US
Short-course therapy	ABECB/ ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
Efficacy with resistant organisms	Pursuing 15 isolates Increased to 25 isolates	Under exploration	Claim for pen-R Strep pneumo (15/15 isolates)	None	Not obtained, pen-R and mac-R (14/17 isolates)
Safety	QT, liver Added 1000 patients	Approved	Approved	Approved	Large database condition for approval US, EU approval

[•]Possibility of a QD follow on is limited

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[•]ASP repeat studies thought to be commercially non-viable

ABT 773 Expected Value based on ABS/ASP results



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Recommend Closing EU ASP Trial

- Indication with 150mg QD lost:
 - **US:** Non-approvable, less than 85% bacteriological cure and less than 10% difference
 - EU: Likely nonapprovable, less than 10% difference to Penicillin and >80% in 2 trials
- Issue is the communication

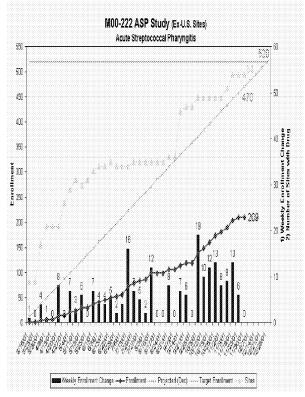


EXHIBIT 614 Part 2

16

M01-325 QT Study Design

- 68 Healthy males and females, 20% greater than 50 years old.
- Double-blind, multiple-dose, four-period crossover each period dosing 5 days, 10 day washout
- Placebo, 150 mg BID, 300 mg BID, 450 mg BID
- Randomized, into 1 of 4 sequences containing

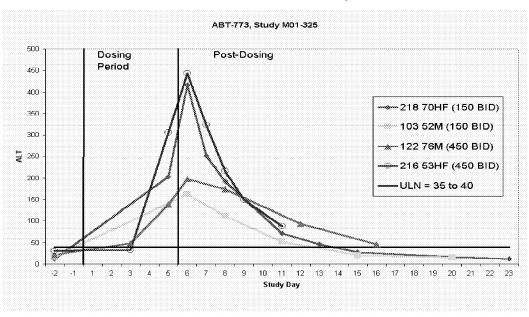


Each period ECG collection:

Day -1 Placebo baseline, Day 1, Day 5 ECG and PK

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Study M01-325: 4 Subjects with Significantly Elevated (>3xULN) ALT (All >50 years old)

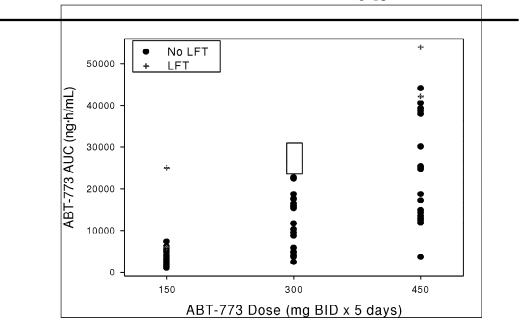


2 subjects at 150mg BID and 2 subjects at 450mg BID

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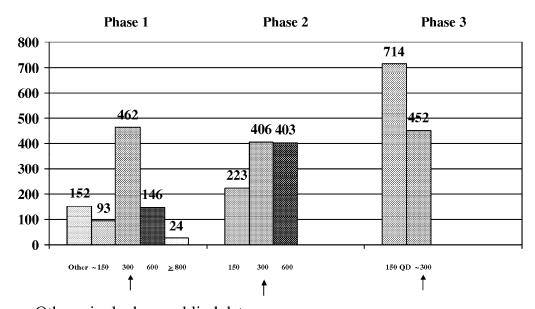
18

Study M01-325: Relationship Between Dose and Day 5 ABT-773 AUC_{0-18}



LFT = Subjects 103, 122, 216 and 218; No LFT = All other subjects.

No. of Subjects Available for Analysis



Other: single dose or blind data

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Overall Incidence of LFT's Not Changed (All Subjects with LFT)

	≥3x ULN
Original overall	39 (1.4%)
N=2884	[1.0, 1.8]
New overall	43 (1.5%)
N=2939	[1.1, 2.0]
Current Phase 3	17 (1.6%)
N=1047	[0.9, 2.6]

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Investigation of the Available Database Exhibits No Concern for Continuing at 150mg BID and 300mg BID **Overall ALT Abnormality Rates in Phase 2 and 3** (Normal at Baseline -- ALT <1x ULN)

	> 1x ULN	≥ 2x ULN	≥ 3x ULN	≥ 5x ULN
150 mg QD	71/738	8/738	3/738	2/738
	(9.6%)	(1.1%)	(0.4%)	(0.3%)
	[7.6, 12.0]	[0.5, 2.1]	[0.1, 1.2]	[0, 1.0]
150 mg BID alone	38/344	4/344	1/344	0
	(11.0%)	(1.2%)	(0.3%)	[0, 0.8]
	[7.9, 14.8]	[0.3, 3]	[0, 1.6]	
300 mg daily	88/667	8/667	3/667	0
(includes 150 mg	(13.2%)	(1.2%)	(0.4%)	[0, 0.6]
BID)	[10.7, 16.0]	[0.5, 2.3]	[0.1, 1.3]	
600 mg daily	59/327	8/327	2/327	1/327
· •	(18.0%)	(2.4%)	(0.6%)	(0.3%)
	[14.0, 22.6]	[1.1, 4.8]	[0.1, 2.2]	[0, 1.7]

[•]Only 24 patients at doses 800mg or above

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[•]Dose response demonstrated increases at 600 mg

ALT Changes at Post-Therapy 1-2 Days After Last Dose (Subjects with Normal at Baseline)

ALT Value	Clari ER* N=783	ABT-773 ^{&} 150 mg QD N=574	ABT-773 [@] 150 mg BID N=328	ABT-773 # 300 mg N=633	ABT-773 ^ 600 mg N=314
>1x ULN	35 (4.5)	50 (8.7)	24 (7.3)	55 (8.7)	39 (12.4)
≥ 2x ULN	3 (0.4)	6 (1.0)	3 (0.9)	6 (1.0)	2 (0.6)
≥3x ULN	0	2 (0.3)	1 (0.3)	2 (0.3)	0
≥5x ULN	0	1 (0.2)	0	0	0

^{*}Clari ER Phase 3, ABECB, ABS and CAP.

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[&]amp;Phase 2 and 3; [®]Phase 3; #Phase 2 and 3, including 100mg TID, 300mg QD and 150mg BID.

[^] Phase 2, including 200mg TID and 600mg QD.

[¶] Number (%)

ALT Changes at Post-Therapy 7-14 Days After Last Dose (Subjects with Normal at Baseline)

ALT Value	Ketek N=1232*	Comparator N=1031*	ABT-773 ^{&} 150 mg QD N=618	ABT-773 [@] 150 mg BID N=302	ABT-773 # 300 mg N=598	ABT-773 ^ 600 mg N=273
>1x ULN	98 (8.0)	92 (8.9)	36 (5.8)	23 (7.6)	46 (7.7)	34 (12.5)
≥2x ULN	6 (0.5)	4 (0.4)	2 (0.3)	1 (0.3)	3 (0.5)	4 (1.5)
≥3x ULN	1 (0.1)	3 (0.3)	1 (0.2)	0	1 (0.2)	2 (0.7)
≥5x ULN	0	0	1 (0.2)	0	0	1 (0.4)

^{*}Ketek Phase 3

[&]amp;Phase 2 and 3; @Phase 3; #Phase 2 and 3, including 100mg TID, 300mg QD and 150mg BID.

[^] Phase 2, including 200mg TID and 600mg QD.

²³ ¶ Number (%)

Maximum ALT Changes in Phase 3 CAP (Ketek, Clari ER, ABT-773)

Studies in Subjects with Normal Baseline Values

ALT Value	Ketek 800 mg QD N=395	Clari ER 1000 mg QD N=121	ABT-773 150 mg BID N=148
>1x	86 (21.8)	14 (11.6)	17 (11.5)
≥2x	14 (3.5)	5 (4.1)	2 (1.4)
≥3x	4 (1.1)	0	1 (0.7)
≥5x	1 (0.3)	0	0

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No "Index" Case to Date in ABT-773

- •Up to 3% 3x ULN LFTs acceptable in antibiotics (CDER-PhRMA-AASLD conference Nov 2000)
- Asymptomatic
- •Reversible
- •No change in bilirubin (Hy's law)
- •No chronicity

Ketek had 2 index cases This can drive an increased database need. Quinalones—5000 patients "Hy's law"—10 000 patients

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Conclusions from Complete Analysis of LFTs

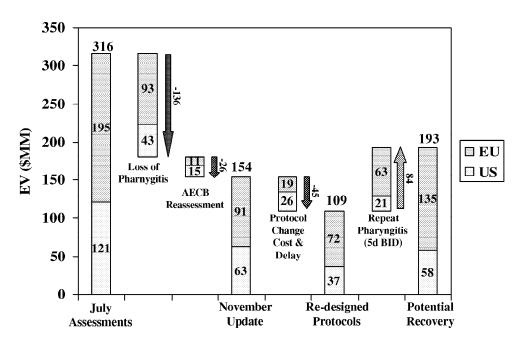
- Overall average event rate is relatively unchanged
 - 4 cases in QT study
 - (7 cases in Japanese bridging study)
- Definite drug effect with possible dose effect (Possible AUC relation)
- No. of patients with $\ge 3x$ ULN ALT well within regulatory acceptable limits for antibiotics at 150mg BID (includes phase 3 trials)

(CDER-PhRMA-AASLD conference Nov 2000)

- No 'index' case to date
- No single clinical identifier of patients at risk
- Recommendations to FDA
 - QT trial to recommence if practicalities allow and data still acceptable
 - Open label without 450mg BID dose
 - Protocol amendments to add Day 6 LFT and changes to informed consent recommended

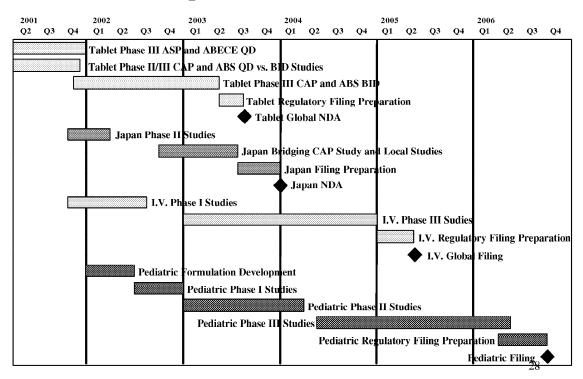
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Current ABT 773 Expected Value Assessment

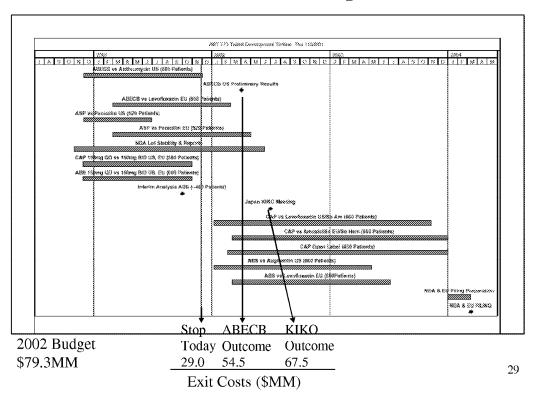


Additional LFT regulatory risk has not been quantified in the above analysis.

ABT-773 Development Program – Tablet, Japan, I.V. and Pediatric Plans



ABT 773 Current Development Plan



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• Back up

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Regulatory experience defined new regulatory standards which determines program size:

- Size of the safety database is driven by the product **benefit/risk** profile:
 - Ketek's 3200 patient safety database insufficient, ?liver/QT.
- A resistance claim will significantly support benefit risk:

Isolates Needed	% CAP patients with PRSP/MRSP		
	1.4%	1.6%	3.2%
17	1236	1063	531
25	1818	1563	781
30	2182	1875	938

• Importance of CAP emphasized

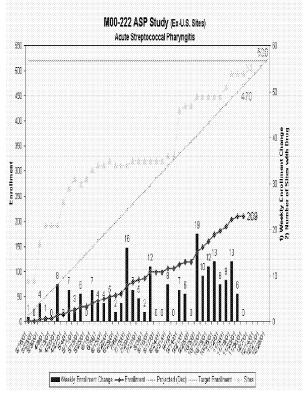
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Six strategic alternatives were evaluated by the team on the basis of technical, regulatory and commercial attributes.

- 1. Complete current ABS & CAP dose-ranging trials and then make dose decision. (Use ABS & CAP dose-ranging data)
- 2. Complete only the ABS dose-ranging study and then make a dose decision for both ABS & CAP. (Use ABS dose-ranging data only)
- 3. Select the BID dose today for ABS & CAP Ph III pivotal. (Select BID today)
- 4. Select the QD dose today for ABS & CAP Ph III pivotal. (Select QD Today)
- 5. Develop BID in CAP & ABS for EU; Develop QD for US. (QD in the US & BID in the EU)
- Expand the Phase III CAP program to allow for 3 arms per study QD vs.
 BID vs. comparator. (Phase III 3-arm CAP & ABS pivotal). Variation: drop
 arm on result availability

Recommend Closing EU ASP Trial

- Indication with 150mg QD lost:
 - **US:** Non-approvable, less than 85% bacteriological cure and less than 10% difference
 - EU: Likely nonapprovable, less than 10% difference to Penicillin and >80% in 2 trials
- Issue is the communication



ABT 773 QT issues

- Re-read key Phase I and Phase II ECG data (6749 ECGs)-completed
- Phase III studies ECGs: Ongoing studies (9085 expected)-45% completed Planned studies (8000 expected)
- Dedicated Phase I QT evaluation study as agreeed by FDA started Sept 01 (>9000 ECGs)
- -Four-period, double-blind, placebo-control crossover design Time-matched ECGs/PK samples at day-1, day1 and steady state on day 5

TOTAL OF 34000 ECG's: Most with correlating plasma levels of ABT773

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